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THE CHICAGO MEDICAL SCHOOL
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DIABETES IN INFANCY AND CHILDHOOD

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The advent of the insulin era changed the outlook for the diabetic child from one of outright hopelessness to one of increasingly greater optimism. Prior to the introduction of insulin the mortality rate was one hundred per cent. Death was staved off temporarily only by a regime of partial starvation. As long as the child lived he remained in a state of constant acidosis. The parents and doctor watched a sick child, almost helpless to do more than wait for his inevitable death. The discovery of insulin shed a shining light on this gloomy situation. Now it is possible to transform a critically ill child into one who approaches clinical normality. If the abnormal physiological changes can not be entirely corrected they can at least be reversed in the direction of the normal state.

Etiology

A hereditary predisposition is the most important factor. In summarizing the available evidence[1] it becomes evident that one-quarter of the siblings of a diabetic child, neither of whose parents have diabetes, will be genetically predisposed to the disease. One-half of the siblings of a child with one diabetic parent will be genetically predisposed, while one hundred *per cent* of the offspring, both of whose parents have the disease, will be predisposed, and given time will ultimately develop frank diabetes. While only twenty *per cent* of the child diabetics in Priscilla White's series have a family history when the disease is discovered, this is increased to sixty *per cent* after twenty years. The absence of a family history is not conclusive evidence of absence of the disease; we must consider the possibility that it went unrecognized, or that a parent or grandparent, while carrying the tendency, did not live long enough for it to have become manifest.

It was long thought that acute infections precipitated the onset of the disease. Measles was particularly suspect as an inciting factor. Analysis of a large group of cases[2] has shown that this is purely coincidental. An acute infection will, of course, immediately increase the severity of a case, and may forcibly bring to attention a mild and previously unrecognized involvement. Whatever the etiological factors the incidence is by no means rare. About five *per cent* of all diabetics are children or one child out of every twenty-five hundred. This means that there are about sixteen hundred diabetic children in the city of Chicago. It is an unusual situation for a busy pediatrician not to have encountered at least one case.

Diagnosis

Glycosuria and hyperglycemia together are the prime requisites for a diagnosis, in the child as well as the adult. In contrast to older persons, where the condition may be mild with little glycosuria and few or no symptoms, the disease in young persons is almost always severe and manifests classical symptoms. In most children the onset is explosive;

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in fourteen *per cent* the development of coma is the first indication that something is amiss. The presence of glycosuria, discovered in routine urinalysis or searched for because of suggestive symptoms, dictates an examination of the blood sugar. Diagnostic levels are values above 130 mg./100 cc. fasting or 200 mg./100 cc. post-prandial in capillary blood. Only rarely in children will a formal glucose tolerance curve be required, and here the *peak* of the blood sugar rather than the duration of the curve is of greater importance. Since starvation tends to elevate the blood sugar, it is essential in a doubtful case that the child have been on an adequate diet for at least three days before blood sugar determinations are made.

Transient glycosuria is very common in children. Renal glycosuria is encountered occasionally. Rarely sugars other than glucose are found in the urine. The differentiation between these conditions and true diabetes is based on the blood sugar determination. This serves to emphasize again the absolute necessity for examination of the blood before the diagnosis is established.

Therapeutic Problems

Two problems in particular contribute to the difficulty of treating a child with diabetes. The first is the inherent severity of the disease, with its tendency to brittleness, *i.e.*, wide swings from hyperglycemia and marked glycosuria to hypoglycemia and insulin reactions. The second is that of enforcing the regimentation and discipline necessary to insure a smooth course. The very young child is more subject to his parents' control, but as he grows and seeks the independence of his approaching maturity he tends to rebel against all forms of discipline. In adolescence, especially, he resents any limitations on his free and easy-going way of life and on anything which interferes with his conforming to the habits of his colleagues. It is during this period that the patient most frequently disappears from the doctor's supervision, only to return at a later period badly out of control.

A basic controversy in the philosophy of treatment exists today. Does the degree of control of the diabetes govern the speed and degree with which arteriosclerotic complications develop? Tolstoi[3] set off this controversy in 1943 when he proposed a marked liberalization in management contrasted with what had been generally accepted up to then. His criteria for adequate management were the following:

(1) Freedom from classical symptoms, such as thirst, polyuria, and itching.
(2) Maintenance of weight, or in children, adequate gain in weight.
(3) Absence of ketosis.
(4) A sense of well being.

Tolstoi offered the following advantages of his plan of treatment. The life of the patient was made much easier with a liberalized diet; weighing and careful measurement of food was no longer necessary. For all practical purposes the patient ate a "free diet," restricting only "free sugars," that is, pastries and confections. Of greatest importance he stated that the presence and degree of arteriosclerotic complications was not greater in a group treated according to this method. Tolstoi's plan of treatment differs, at least in theory, from the classical method so strongly advanced by, among others, Joslin and his group in Boston. Here an attempt is made to approach normal physiological conditions as closely as possible, with absence of glycosuria, as well as persistent normoglycemia. The diet is carefully outlined, and the food is weighed. Frequent checks are made on the urine and blood. In actual practice these two proponents are not as far apart as would at first appear. Treatment which fulfills Tolstoi's dicta comes very close to satisfying Joslin's requirements. In order to achieve the absence of symptoms which Tolstoi requires, glycosuria must be minimal and blood sugar not too high, for hyperglycemia will be followed by glycosuria with constant loss of water, polyuria, and then inevitably polydipsia. The loss of calories associated with considerable glycosuria limits the amount retained for nutritional purposes and results in loss of weight.

Dietary Control

Dietary requirements for the diabetic child do not differ from those in any other normal child of the same age, and include adequate calories, adequate protein, and adequate vitamins and minerals. A one year old infant requires about 1000 Calories a day for maintenance and growth, with a 100 Calorie increment each year up to maturity, about age thirteen for girls and seventeen for boys. While one gram of protein per kilogram of body weight per day is an optimum intake for the physically mature individual, the actively growing child who is rapidly laying down protoplasm demands a higher figure, on the order of between two and three grams of protein per kilo per day. Sufficient milk, fruits, and vegetables to satisfy the mineral requirements, and accessory vitamin concentrates are included. The only fundamental difference is the interdiction of free sugars. With this exception the child can be offered the same well-balanced diet that would be offered to any other child. Careful attention to the weight and growth curves will indicate whether the diet is adequate. In beginning treatment my practice is to outline such a normal diet, indicating in household measurements the quantity in those few foods which contain concentrated carbohydrates and fats, *i.e.*, cereal by the cup, bread in slices, and butter in restaurant-sized squares. In addition to the three standard meals a bed-time snack is always required to prevent early-morning hypoglycemia, and in most cases a mid-morning and mid-afternoon allowance to prevent pre-meal hypoglycemia. As time goes on the patient gradually develops the habit of eating the same quantity of food daily, so that regulation of intake becomes almost automatic, and he can eat out as a guest or in a restaurant with little or no difficulty.

Insulin Requirements

While the adult with mild disease can be managed without insulin, no such allowance is possible for the child. Insulin is mandatory for the juvenile diabetic. The choice of type of insulin and the dose are a matter of trial and error, but certain principles will guide the ultimate prescription. Quick acting regular or crystalline insulin is usually preferred for initial treatment when the diagnosis is first made. This is given on a four hour schedule during the day, the dose depending on the results of spot urinalyses for sugar. For a very young child the dose may vary between three and five units for a one to four plus glycosuria. In the older child the dose may reach twenty-five units for a four plus glycosuria. As soon as the symptoms and excess glycosuria are under control some type of depot preparation is substituted. While better control can more easily be achieved with multiple doses, psychologic reasons dictate an attempt to limit insulin to one daily administration. Three choices are available: protamine zinc insulin, NPH insulin, or a mixture of protamine zinc insulin or NPH with regular insulin. Globin insulin in most cases has too short a duration for full twenty-four hour control with one injection. NPH insulin has the advantage over protamine zinc insulin of offering a rapid daytime action with a diminishing effect at night. It has an action similar to that of giving a dose of protamine zinc insulin to which is added a separate dose of regular insulin half the amount of the protamine zinc insulin. Since there is no excess of protamine in NPH insulin, regular insulin added to it is not bound and retains its quick-acting effect; this addition may be made if daytime glycosuria becomes a problem. Protamine zinc insulin alone is usually not adequate except in the mildest of cases because its constant effect through the whole twenty-four hour period will either keep night-time glycemia normal but permit excess glycosuria in the post-prandial periods, or with a larger dose control post-prandial glycosuria but result in night-time hypoglycemia. To offset this, mixtures of regular insulin and protamine zinc insulin may be used. Since the excess of protamine in protamine zinc insulin will convert added quick-acting insulin to a depot insulin, a large quantity of regular insulin must be added before all the excess protamine is neutralized. The most com-

monly used of such mixtures is two parts of regular insulin to one part of protamine zinc insulin, which is similar in effect to that of NPH alone. This can be changed to balance day-night action. If daytime glycosuria is difficult to control the amount of regular insulin can be raised to two and one-half or three parts to one of protamine zinc insulin. Once a depot preparation is given it is imperative that the child eat in order to make use of the insulin. Meals must be offered on time, and hypoglycemia will indicate the need for the between-meal snacks. The increase in dosage which will be required as time goes on reflects the child's growth and does not indicate increasing severity of the diabetic state.

Exercise is as important to the diabetic as it is to any other child. It has the further effect in the diabetic child of promoting the utilization of glucose, and in this way parallels the action of insulin. Because of this it is advisable to plan the between-meal feedings so they come before the child's play periods, in order to avoid insulin reactions.

The Psychological Problem

No discussion of treatment would be complete without a consideration of the psychological factors in both child and parent. Limitation of diet, no matter how mild, differentiates the patient from his friends. It is essential to emphasize to the child how important continued treatment is. This must be done in as kindly and persuasive a manner as possible, so that he will understand why he cannot entirely conform to his friends' habits. Permissive attitude in other fields of behavior may ameliorate his attitude towards the restrictions required for his management. Allowing some high-gratification foods such as cake and ice-cream at occasional birthday parties will ease the child's distress. I have found that giving the child responsibility for his management at an early age gives him a sense of pride and accomplishment which often permits better control than when the parent does it all. The child should self-administer his insulin, learn to do urine tests, and understand his dietary requirements just as soon as his intellectual and manual development permit. This can often be accomplished by the age of eight. The reaction of the parents to a diabetic child varies. They may feel guilt. They tend to overprotect and overindulge the child. They may attempt to shield him and keep the diabetes a secret within the family unit, and they are always grossly fearful of complications. Meeting with other parents in the same predicament has been helpful and I have arranged such meetings where three or four mothers get a chance to discuss their mutual problems with a considerable easing of their tensions.

Ketosis

Theoretically the properly managed diabetic patient should never go into acidosis or coma. When this occurs it is due to a relative insulin deficiency. This may be caused by absolute omission of the medication or some change in the patient's condition, such as an infection. With lack of insulin there is impaired glycogenesis and loss of glycogen from the liver. The liver cells then metabolize more fat and the production of ketones increases beyond the ability of the body to utilize them. Increased catabolism of tissue cells occurs with the liberation of labile intracellular components into the plasma, and then into the urine. The increased urinary excretion of phosphate, potassium, and sodium leads to increased acidosis, inability of the body to hold water, and progression of the dehydration. In children, whose livers are proportionately small in relation to their body size, the supply of glycogen is also small, and the ease of production of acidosis is correspondingly great. Return to normal depends upon: (1) Effective insulin action, (2) Rehydration, and (3) Replacement of lost salts. While the presence of acetone in the urine is in itself no cause for immediate hospitalization, it is a signal to start corrective measures. The parents should be taught to do a simple spot test for acetone and should be instructed to test the urine whenever the child has an infection. Simple treatment will be effective in most cases. The diet should be

limited to easily assimilated foods; chiefly broth, fruit juice, cereals, eggs, and milk—with a feeding every hour or two. The urine should be examined for sugar and acetone every two hours. If four plus reactions are found for both, regular insulin is given in addition to the basic morning dose. If acetone is found with a negative or one plus sugar reaction, orange juice is given and insulin omitted. For a one or two plus sugar reaction alone, insulin is omitted. For greater degrees of glycosuria alone an additional dose of regular insulin is administered. In the treatment of mild degrees of acidosis, salt replacement is adequately handled by giving broth along with the salt usually used in foods, and potassium loss is replaced by the potassium in foods, especially orange juice.

Hypoglycemic Reactions

Insulin reactions are likely to develop most commonly after a period of exercise. Prevention is best practiced by a feeding before any unaccustomed exertion. Reactions to depot insulin may occur insidiously, and may be manifested by a change in disposition. Undue crankiness is sometimes the first indication that the blood sugar is dropping. Orange juice or a piece of sugar or candy will usually alleviate the symptoms quickly. If the child cannot swallow, the parents should be trained and prepared to give three to five minims of 1:1000 adrenalin subcutaneously. If all of this fails it may be necessary to give glucose intravenously. Once the hypoglycemia has been alleviated the child should be fed some slowly utilized food containing protein and fat, or the hypoglycemia may recur as the quickly available carbohydrate is utilized.

Arteriosclerotic Complications

As the expectation of life for the diabetic increases, the long term problem of arteriosclerotic complications has come to attract more and more attention. There is a general agreement that duration of the disease is itself a factor in the genesis of arteriosclerosis. A study of a large group of patients whose diabetes had been present for from twenty to twenty-four years yielded the following results:[4]

COMPLICATION	PER CENT
Gangrene	2
Pulseless feet	11
Calcified arteries	88
Blindness	10
Proliferating retinitis	58
Non-proliferating retinitis	94
Cerebro-vascular accidents	4
Myocardial damage	18
Hypertension	40
Nephritis	37

Up to about fifteen years duration little or no arteriosclerosis can be detected. Beyond this, as the table indicates, some degree of vascular damage is almost universally present, with non-proliferating retinitis present in ninety-four *per cent* of all patients. It is about this period, where the diabetes has been present for over twenty years, that the controversy exists between the advocates of tight versus loose control, as to the greater efficacy of rigid control in preventing the more severe complications. Wilson[5] and his colleagues compared three groups of patients, all with diabetes of over twenty years duration. In their well-controlled group forty-six *per cent* had evidence of severe retinitis, while seventy-four *per cent* of those on a free diet with no attempt at chemical control and eighty *per cent* who had been in coma (which is used as an indication that their management was very poor) had similar complications. The combination of retinitis and advanced lesions of the peripheral vessels was twice as common in the free and coma groups as in the controlled group, with twenty-eight *per cent* in the controlled patients, fifty-seven *per cent* in the free group, and sixty-five *per cent* in those who had been in coma.

In another publication[6] the same authors report no case of diabetic nephropathy in patients with good or excellent control after twenty to thirty-four years of diabetes, while a substantial percentage of those with only fair or poor control demonstrated this complication. Similar results are reported by others,[7,8,9] all agreeing that while duration of the dia-

betes is a factor, the incidence of retinitis and other vascular complications is more prominent in those whose management is poor.

This evidence seems to lead to a clear and irrefutable conclusion; good control, for the most part, results in less vascular disease. Good results can be achieved by proper insulin prescription and the use of a free diet, if symptoms are controlled so that the levels of glycosuria and glycemia are also then necessarily maintained close to normal. Since good chemical control is then achieved, the apparent conflict between the proponents of controlled versus free dietary treatment is resolved.

CASE REPORTS

Case 1. E. A. Diabetes was discovered in 1929 when she was fourteen years old. She was treated initially with regular insulin in fractional doses, but still had frequent insulin reactions and episodes of marked hyperglycemia and glycosuria. When protamine zinc insulin was introduced she was treated with one dose of this preparation daily. At the age of twenty she developed acute appendicitis, and although she ran a very stormy course, recovered satisfactorily from the surgical procedure.

In April, 1941, she had a spontaneous abortion which was accompanied by profound coma. In retrospect it was evident that recovery from the coma was complicated by potassium deficiency, although she was not given potassium. Following this she was treated with twenty units of protamine zinc insulin and ten of regular insulin in separate injections before breakfast and five units of regular insulin before dinner. Somewhat later this was changed to ten of protamine zinc insulin and twenty units of regular insulin in one syringe before breakfast. By December of 1946 her requirements had increased to thirty-three units of regular insulin and seventeen units of protamine zinc insulin in one syringe. Although the fasting blood sugar on random determinations was close to normal, 133 mg./100 cc. in December, 1946, and 118 mg./100 cc. in May, 1947, she continued to be fairly unstable with frequent episodes of marked glycosuria.

In June, 1947, she had pleurisy; at this time her control was poor with a fasting blood sugar of 350 mg./100 cc. and traces of acetone in the urine. In September, 1947, an epithelioma of the cheek was discovered. This was treated with x-ray with no break in control. In May, 1948, a severe upper respiratory infection also occasioned a break in control but this was quickly corrected. Insulin dosage at this time was twenty-eight units of regular insulin and twenty-two units of protamine zinc insulin in one syringe. By July of 1952 she had been switched to NPH, fifty units each morning. She still tended to have brief periods with marked glycosuria, but these were less frequent and lasted only twelve hours at most. Urinary frequency was her clue to excess glycosuria.

In March of 1953 she was thoroughly studied for evidence of vascular changes. Blood pressure was 124/82. The eye grounds were reported by a competent ophthalmologist to be entirely normal. There was no evidence of calcification of the blood vessels on x-ray examination. The urine was free of albumin and fixed elements, and the electrocardiogram was normal. This examination will be repeated this year, and if the results are as satisfactory she will be eligible for the American Diabetes Association twenty-five year medal.

Comment: Although this woman's diabetes was unstable, requiring many adjustments in management, she remained in good control most of the time although on a free diet. Her one episode of coma was due to a severe intercurrent complication and did not follow carelessness in treatment. Now at the age of forty, after twenty-five years of diabetes, her vascular structure appears to be as good as a non-diabetic of the same age.

Case 2. M. S. This man was examined for the first time in December, 1945, when he was fifty years of age. He had consulted the referring ophthalmologist because of difficulty in vision which he believed could be corrected with glasses. Examination had then disclosed a severe

retinitis. He gave a history of known diabetes of twenty years duration. This had always been mild, and he had treated himself without consulting a doctor for several years, varying his insulin dosage from ten to fifteen protamine zinc insulin a day, taking the larger dose when his urine showed sugar and reducing the dose when the reaction was negative.

Except for the fact that he was about twenty pounds over ideal weight, physical examination was otherwise negative. Initial fasting blood sugar was 142 mg./100 cc. With a reduction diet his weight came to normal and he was able to discontinue insulin entirely while maintaining normal fasting blood sugars and with the urine staying consistently sugar-free. In spite of this, when last examined in November, 1946, his retinitis had progressed so that he was almost totally blind.

Comment: Although this man reported that his diabetes had always been mild, and was easily and well controlled, a fact which seems reasonable in view of the virtual disappearance of his diabetes with weight reduction, the duration of the condition alone seems to have been enough to have brought about an inexorable progression of proliferating retinitis to the point of complete loss of vision.

Summary

1. Juvenile diabetes is usually a severe form of the disease, with a tendency to marked instability characterized by frequent swings between insulin reactions and prominent degrees of glycosuria.

2. Treatment is directed at relieving classical diabetic symptoms, preventing ketosis, and insuring adequate growth and development. An attempt is made to achieve these ends with one dose of insulin daily.

3. Complete control of symptoms will be accompanied by physiologic conditions reasonably close to normal, with absent or minimal glycosuria. This can be achieved by permitting the patient a free diet, with limitation only of free sugars. This method of treatment can insure both good clinical and chemical control, and will defer and limit the development of arteriosclerotic complications.

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DIARRHEA IN INFANCY AND CHILDHOOD

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Introduction

Diarrhea in infancy continues to be one of the major medical problems encountered in this age group, particularly in children under one year of age. Diarrhea and enteritis now constitute the fifth most frequent cause of death in infants under one year of age. The disease is almost as prevalent in the winter as in the summer, but in large congested cities, more cases are reported during the warm months. Enteritis is the disease most feared in a nursery and in hospital wards caring for sick infants.

Etiology

Causes of diarrhea in infants and children are extremely variable. The Salmonella organisms, *Endamoeba histolytica, Proteus morganii, Pseudomonas aeruginosa,* and others have all been isolated from stools of young infants during epidemics and sporadic cases of diarrhea. In other instances, organisms not considered pathogenic in adults have been found in large numbers in the stools of infants with gastro-intestinal symptoms, which suggests that these organisms, under certain circumstances, may be pathogenic for young infants.

Netter, Korns, and Trussel[1] demonstrated the presence of *Escherichia coli,* sero group 0111, as the predominant coliform organism obtained from seven infants who were suffering from epidemic diarrhea of the newborn. Lyon and Folsom[2] noted epidemics of diarrhea in association with influenzal infections prevalent in the community and in which transfusions of blood from adult donors ameliorated the gastro-intestinal symptoms in the young patients. Although the virus was not isolated from the stools of these patients, the circumstantial evidence incriminated the virus of influenza. Light and Hodes[3] were the first to fulfill Koch's postulates with a virus isolated from the stools of babies which was successfully transferred intranasally into calves. Buddingh and Dodd[4] have contributed extensively to our present concept of viral etiology in gastro-enteritis in infants and children. Other etiological agents such as food allergy, dietary indiscretion, parenteral infections, celiac syndromes, which include fibrocystic disease of the pancreas, starch intolerance, and celiac disease, as well as anatomic and chemical causes, have all been documented at one time or another as the cause of diarrhea in the pediatric age group. Wegman[5] reported an outbreak of diarrhea in a newborn nursery which evidently was a reaction to boric acid. Pledgets of cotton soaked in boric acid solution were used in pre-nursing cleansing of the mothers' nipples. When this procedure was eliminated, the diarrhea stopped.

Pathology

No characteristic pathological lesions have been reported. The intestines may show nothing except a mild non-specific leucocytic infiltration. Peyer's patches may be thickened and the intestinal mucosa may be congested and reddened, but ordinarily there is little evidence of local infection. Dysentery organisms may, at times, produce wide-spread mucosal ulcers, but not as a rule.

Signs and Symptoms

Usually an attack of gastro-enteritis is quite characteristic and is manifested by the sudden onset of diarrhea with as many as twenty or more stools a day. The mechanism for this hyperperistalsis is not well understood, but the principle of purging to remove irritants in the gastro-intestinal tract has been almost completely abandoned.

Loss of weight, which invariably occurs, is due to the rapid emptying time

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which does not allow enough time for adequate absorption. Even more important is the damage to the assimilatory mechanism, reflected in the faulty assimilation of water, sugar, fat, and to a lesser extent, minerals. All of this abets the loss of weight, dehydration, and acidosis. Protein, for some reason, is not involved in this process and even the most marantic infant continues to assimilate protein and remain in relative positive nitrogen balance.

Vomiting of feedings is quite frequent. The stools are watery and may or may not contain blood, mucus, or both. High, moderate, and sub-normal temperatures have been recorded. Soon evidence of dehydration sets in as manifested by a depressed or sunken fontanel and poor tissue turgor. In addition, the eyes appear sunken, the cornea loses its lustre, and a film of mucus appears to cover it. The loss of weight, partly due to the loss of extra-cellular fluids may give rise to either an "hyper-electrolytemia" if there is a greater loss of fluids than electrolyte, or an "hypo-electrolytemia" if the opposite is true. Shock is sometimes disclosed by cold, clammy skin, cyanosis, drop in blood pressure, tachycardia, oliguria, or a pre-renal azotemia which suggests, but does not prove, an hypo-electrolytemia. Acidosis becomes evident by the acetone odor of the breath, the presence of acetone in the urine, Kussmaul breathing, drop in pH and carbon dioxide combining power of the blood.

The mechanism of this acidosis has been debated by biochemists for many years and although definite decisions are not agreed upon, the following are probably involved:

1. Over-production and/or decreased utilization of the ketone bodies;
2. Accumulation of lactic acid;
3. Chloride acidosis, due to a greater loss of base . . . the greatest loss of this base being the exchange of sodium for potassium into the cells [6, 7].

Cerebral symptoms varying from marked restlessness and meningo-encephalitic manifestations to apathy and listlessness are quite common and have been ascribed to the cerebral anoxia and dehydration.

Complications

Infections of one kind or another are the most frequent complications of diarrhea. Whether the infection causes the gastro-enteritis or whether the lowered resistance due to the diarrhea gives rise to the infection cannot always be decided, but both mechanisms probably operate.

Nutritional failure is a common and usually serious complication. Holt[8] believes the over-zealous efforts to check the diarrhea by therapeutic starvation contributes to this picture. Chung and Holt[9] used early oral feedings as a supplement to parenteral therapy. They base their recommendations on evidence that the intolerant intestine absorbs more food when more is given and that recovery of tolerance is not delayed by oral feedings. Most physicians, however, are reluctant to use this mode of therapy. Because of the availability of more effective methods of maintaining adequate fluid, electrolyte, and caloric balance by parenteral methods, they adhere to the older method of putting the gastro-intestinal tract at rest by withholding all oral feedings.

Cerebral sinus thrombosis, renal vein thrombosis[10], and other venous thromboses have been reported complicating severe infantile diarrhea. Whether the infection or the marked hemo-concentration or other factors not quite understood are responsible for these venous thromboses has not as yet been elucidated.

The occurrence of tetany in cases of diarrhea, especially during treatment, has been noted by many observers. The mechanism of its production has been explained by:

1) decreased absorption of calcium and increased loss of calcium from the intestinal tract due to the rapid emptying time;
2) decreased absorption of calcium due to the steatorrhea;
3) reduction of ionized calcium due to azotemia;
4) mobilization of calcium from the skeleton (osteoporosis), with subse-

quent excretion in the feces and urine;

5) rapid redeposition of calcium in the bones during treatment and cessation of the diarrhea, thereby exaggerating the existing hypo-calcemia.

Other complications such as purpura, sclerema, and edema are encountered, but rather infrequently.

Treatment

The treatment of diarrhea depends upon the etiological agent involved, the severity, the presence or absence of constitutional symptoms, the electrolyte imbalance, and the degree of dehydration.

Mild diarrhea may often be treated successfully by a reduction of food intake or actual starvation except for the use of sugar water or carbonated beverages for twenty-four hours or longer. Usually no other treatment will be necessary, but if the diarrhea persists, an antibiotic combined with a mild antispasmodic may be tried.

Cases with severe diarrhea should be hospitalized and there the treatment should be directed with the following in mind:

1) an antibiotic for a specific etiological agent when possible;
2) correction of electrolyte and fluid imbalance;
3) prevention and/or treatment of acidosis, azotemia, and tetany;
4) replacement therapy when possible (fibrocystic disease of pancreas);
5) deletion therapy when possible (allergic diarrhea, celiac disease, etc.).

In spite of a great deal of work with various antibiotics there has appeared none which can be depended upon in all cases of non-specific diarrhea. In fact, even the specific diarrheas do not have a universally accepted form of treatment.

Sidney Ross et al.[11] reported that Aerosporin (Polymyxin B) in doses of two mg. per kilo every four hours for four to ten days was particularly useful in cases of non-specific gastro-enteritis. Toxic manifestations, however, were quite common, especially with intramuscular administration.

Elmer Kadison and Maxwell P. Borovsky[12] gave Neobacin (10,000 U. neomycin, 2,000 U. Bacitracin) tablets to infants under one year of age with diarrhea. Some of these infants had specific infections; in others no etiological agent was demonstrated. In all, the results were uniformly good and no toxic manifestations due to the drugs occurred.

Ralph H. Kunstadter and Lawrence Breslow[13] discussed the use of Terramycin, Sulfadiazine, Chloromycetin, Streptomycin, and Polymyxin B in both specific and non-specific enteric infections, but did not decide which, if any, was the drug of choice.

Charles Goldenberg, William Shlaes, and Sidney Mintzer[14] reported the use of Bacitracin, iodinized Bacitracin, and Diodoquin in the treatment of amoebic dysentery. The rate of relapse was about the same for each drug used.

The value of parenteral fluids, i.e., blood, plasma, protein hydrolysates, and the various electrolyte—containing fluids in the treatment of severe diarrhea in infants is generally accepted. However, the amount and type of fluid to be used varies to a considerable degree. The consensus of opinion obtained from several good sources[15,16], is as follows:

First day:

1. Forty cc. per kilo of a mixture of equal parts of physiological saline solution and 5 to 10% glucose in water intravenously, followed by
2. Thirty cc. per kilo of blood or plasma.
3. Eighty cc. per kilo of a special electrolyte mixture* administered by subcutaneous drip requiring four to six hours for that day's dose.
4. Eighty to 100 cc. per kilo of 5 or 10% glucose in water intravenously to maintain water for insensible loss.

Second day:

1. 100 cc. per kilo of 5 or 10% glucose in water intravenously.

* The special electrolyte mixture can be prepared with 4 Gm. NaCl, 2.7 Gm. KCl, and 50 cc. of molar sodium lactate diluted to one liter.

2. Fifty cc. per kilo of the special electrolyte mixture (as above) subcutaneously.

Third day, etc.:

1. 150 cc. per kilo of a solution containing one part special electrolyte mixture and two parts 5% glucose in water orally, or
2. 150 cc. per kilo of a mixture containing whole milk diluted with water and with sugar added to make a 10% carbohydrate mixture, giving twenty calories per kilo per day and gradually increasing the milk and decreasing the water until one reaches 100 calories per kilo per day.
3. To promote retention of K, the milk mixture providing less than seventy calories per kilo per day is fortified with 1.0 Gm. KCl to that day's mixture.
4. If tetany sets in during correction of the diarrhea, it should be treated with ten or twenty cc. of a 10% calcium gluconate solution intravenously, injected very slowly.

It should be noted that the guide to therapy is the clinical course more than the chemical course.

Fibrocystic Disease of the Pancreas

Treatment of the conditions included in the celiac syndrome require a little insight into the pathogenesis of the diseases included in this syndrome. Fibrocystic disease of the pancreas has a definite familial incidence, and is more common in white children. In early life the manifestations are those of intestinal obstruction due to inspissation of meconium. Those that survive this period will sooner or later develop symptoms referable to the gastro-intestinal and respiratory tracts. The respiratory symptoms, usually those of a severe bronchitis, atelectasis, pneumonia, or pulmonary abscesses, occur before the age of six months. At times mild gastro-intestinal symptoms may be interspersed with those in the lung. In some, the symptoms may be those of chronic indigestion with foul, bulky stools, steatorrhea, and failure to gain weight. Diagnosis is difficult at times, but if the condition is kept in mind, it will often be recognized. History in a family, persistent respiratory symptoms coupled with digestive disturbances and malnutrition, low serum carotene level, Vitamin A concentration below thirty units per cc., decrease in serum cholesterol, failure of feces to digest gelatin in various dilutions, flat Vitamin A absorption curve, and last, but certainly not least, the assay of trypsin from duodenal juice will suggest the diagnosis of fibrocystic disease of the pancreas.

Treatment is directed toward maintenance of nutrition and the prevention of respiratory infection. Since very little of the dietary protein is absorbed, high protein diets are recommended. In many instances fat absorption is also impaired, presumably because of a deficiency of lipase, and also because the quantity and quality of bile is affected. This, in turn, affects the absorption of the fat-soluble vitamins. The question of giving excess or limited fat in the diet has not been settled. Andersen and others advocate the restriction of fats in the diet because they believe it produces a diarrhea which, in turn, aggravates the entire picture. Holt and May, on the other hand, recommend large quantities of fat in the diet because more is then absorbed with a concomitant greater absorption of Vitamin A and a better nutritional state. The use of antibiotics both therapeutically and prophylactically is generally accepted. Substitution therapy has, at times, been helpful, but destruction by gastric juice and unpalatability have reduced its over-all usefulness.

In summary, the following methods are indicated in the treatment of fibrocystic disease of the pancreas:

1) Prophylactic use of an antibiotic during the fall and winter months;
2) Therapeutic use of antibiotics, based on sensitivity during the exacerbation;
3) Use of high protein, and probably high fat diets;
4) Use of parenteral water-soluble vitamins, and

5) Use of replacement therapy, at times.

Celiac Disease

Celiac disease primarily is a rare familial disorder of intestinal assimilation associated at times with a high familial incidence of diabetes mellitus. Like fibrocystic disease, there is no predilection for any sex, and white children are more prone. Unlike fibrocystic disease, the digestive enzymes are present in almost normal quantity. The defect in assimilation primarily affects fat and carbohydrates. The absorption of protein in the celiac patient is practically normal, but hypo-proteinemia and edema are not uncommon. An explanation of the latter is still lacking. The usual onset is manifested by symptoms of nutritional deficiency, commencing with a diarrhea. Vomiting associated with a persistent upper respiratory infection occasionally is seen. The appetite remains poor, weight gain is slow, and the stools become bulky, fatty, and foul smelling. These symptoms may begin in early infancy, but usually appear after six months of age. Breast feeding for some reason or other does not prevent the disease, but seems to postpone the onset of symptoms. As the condition persists, the picture of chronic malnutrition, *i.e.*, loss of subcutaneous fat, especially from the legs and buttocks, and loss of muscular tone with a large, protuberant abdomen, is established. Exacerbations of the disease are quite common, with a marked loss of weight and severe dehydration. At times, these exacerbations can undo in a day or two all the improvements that have been made. These exacerbations are termed "a celiac crisis" and at times can be predicted by a sudden unexplained drop in serum protein. The course of the disease is variable. It may only last a short time, and, on the other hand, may persist until adulthood and even beyond. Some observers think that non-tropical sprue of adults is a persistence or a late exacerbation of the celiac state.

Laboratory aids in the diagnosis of celiac disease are not specific; however, some are more helpful than others. The accurate estimation of steatorrhea depends on the daily fecal loss of fat, which in an average diet rarely exceeds two grams a day. The Vitamin A absorption-curve, which is usually flat in celiac disease, gives an overall picture of the absorption of all fats. The flat glucose tolerance curve is encountered in celiac disease, but is by no means specific. Decreased pancreatic amylase in the presence of normal trypsin and lipase is quite characteristic.

Successful treatment of celiac disease depends upon the breaking of the vicious cycle perpetuated by infection and exacerbation. Most of the treatment aimed at preventing exacerbations, however, has hovered around the ideal type of diet. Protein, since its assimilation is not affected, is given in large quantities. The amount of fat and carbohydrate in the diet, on the other hand, has not been universally decided. Sheldon and Lawson[17] demonstrated that children with celiac disease can absorb more than half their dietary fat, and conclude that excluding fat from the diet prevents their absorbing any fat at all. Others, who restrict fat, base their contention on the hope that partial rest of the disordered function of fat absorption will promote recovery. In regard to the starches in the diet of the celiac patient the status is even more perplexing. Some think monosaccharides are better tolerated than disaccharides; that equal quantities of dextrose and levulose, as found in bananas, are particularly useful; and that cereals, especially wheat and rye, induce a loss of tolerance to fat. Recently, however, it has been shown that wheat gluten is the offending agent, and when eliminated from the diet of celiac patients, they get along better than ever before.

In summary the treatment of celiac disease consists of:

1) prophylactic and therapeutic use of antibiotics;

2) use of parenteral water-soluble vitamins; and

3) proper diet, including from 60-90 calories per pound per day, with

high protein, high fat, and absent starch early in treatment, progressing to a diet with high protein, normal fat, and normal carbohydrate, but one in which "gluten" is excluded. The difficulties in maintaining an entirely gluten-free diet outside of a hospital should be appreciated.

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CURRENT CONCEPTS OF RABIES

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Rabies has long presented a problem to man. Records indicate that it was recognized nearly 4,000 years ago and that the relationship between this disease in man and the bite of a mad dog was known at that time. In spite of this, surprisingly little progress has been made in the control of the disease. Rabies is still widespread in the world, except for two or three small areas, and, although a vaccine has been available since the days of Pasteur, other auxiliary methods of control have not been consistently applied.

A great body of literature has been written about rabies, one recent textbook listing references to upwards of eight hundred articles dealing with the disease. To review these is undesirable, if not virtually impossible. What is to follow is an attempt to summarize the most important points as they are known today.

CAUSATIVE AGENT AND DISEASE

Rabies is caused by a filterable virus which appears to be essentially neurotropic. The virus has a wide host range, infecting mammals as well as fowl and some cold-blooded species. The disease is characterized by a very high fatality rate in most species affected. In man, no recovery of an individual once showing symptoms has ever been recorded with certainty. In other mammals, recoveries are doubtful once symptoms have appeared, although a few such reports have appeared with dogs infected in the laboratory.

Natural infections with the rabies virus occur by means of bites or scratches inflicted by a rabid animal, in which the virus is introduced into the wound. It is necessary that a break in the skin occur, since the virus does not appear capable of penetrating the unbroken skin. The virus remains localized at the site of introduction for some time, estimates running as high as twenty-four hours. This, of course, indicates that local treatment of a wound is highly desirable and indeed, experimental and practical results show that cauterization with strong acid or thorough scrubbing with twenty *per cent* green soap solution are quite effective if applied early. Such treatment is of possible benefit for as long as twenty-four hours after a bite or wound is inflicted.

Evidence indicates that the virus must gain access to nervous elements and that it then travels up the nerve fibers to the spinal cord and brain. So far, no conclusive evidence is available to indicate blood stream transport of the virus.

Incubation Period

The incubation period, both in experimental infections and in those produced by the bite of rabid animals, depends on the site of infection and the amount of virus introduced. Thus, in dogs infected in the lower extremities, the incubation period may be several weeks or even months, while those infected in the masseter muscles may show symptoms in ten days. This has been interpreted as indicating nervous rather than bloodstream transport of the virus. In humans, the average incubation period of rabies varies from fourteen days to nine months, with occasional reports of incubation periods of two to three years. It would appear that the length of the incubation period is more closely associated with the amount of inoculation and the innervation of the area infected, rather than the distance it must travel to reach the brain.

The virus spreads not only towards the brain, but becomes distributed throughout the nervous system. In the course of its spread, it reaches the salivary glands and appears in the saliva of most infected animals a few days before the onset of symptoms. In the dog, this may be three to five days before clinical signs

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of the disease appear. Thus, it is essential that dogs that have bitten humans be held for observation for seven to fifteen days before being released or destroyed. The virus does not always appear in the saliva of infected animals. In dogs, the percentage is quite high.

A few days before symptoms occur, the virus also appears in the brain, where it multiplies and produces damage to the brain cells. In various parts of the nervous system, there appear in the affected nerve cells, characteristic acidophilic, intracytoplasmic inclusion bodies, the Negri bodies, first described in 1903. These bodies appear in greatest numbers in Ammons horn of the dog, but in other animals occur in greatest numbers in other parts of the brain. The characteristic Negri bodies contain basophilic granules which distinguish them from the inclusion bodies of dog distemper and the cat and the mouse bodies that may normally occur in these species. The typical Negri body is diagnostic of rabies infection, and, if properly stained, can be easily recognized by an experienced worker.

The various species of animals vary in their resistance to rabies infection by natural routes. Man appears to be relatively resistant as indicated by a number of studies. Although such information is difficult to obtain, it has been variously estimated that only five to fifteen *per cent* of humans bitten by rabid dogs develop rabies when not given prophylactic vaccination. These figures do not tell the whole story, since the site and severity of the bite have a great influence on the final outcome. Thus, of individuals bitten severely about the head and neck, a high percentage develop the disease, while of those bitten about the legs, a much smaller number are affected. Other animal species vary in susceptibility, some being more and some being less susceptible than man.

EPIDEMIOLOGY

Observations made within recent years in Central and South America are of considerable interest as are some quite recent observations in the United States. This involves the presence of rabies in bats. It has been found that the vampire bat is naturally infected in wide areas of Central and South America. The disease in these animals is of considerable interest since it runs a more chronic course, and the bat can carry the virus in its saliva for extended periods. A great deal of economic loss results from the infection of domestic animals as a result of the bite of these bats. Occasional human infections occur following attacks by infected vampire bats, since during the active stage of the disease, the bats fly in daytime. Most infected bats evidently die of the disease after more or less prolonged periods of infectivity. The form of rabies resulting from the bat virus differs somewhat from the classic disease resulting from the bite of rabid dogs.

Rabies virus has also been isolated from insectivorous bats in Central and South America. Such bats have been known to attack human beings during the active stage of their disease. So far, little is known about the maintenance of the disease in such bats. It is likely that the disease is transmitted from bat to bat in nature and constitutes a real reservoir of infection in these areas.

Recently, bat rabies virus has been isolated from insectivorous bats in Florida and Pennsylvania. In both instances, a bat made an attack upon a human. Such observations may indicate new complications with this disease. It is not yet known whether the virus is widespread enough in bats in any areas of the United States to constitute a reservoir, or whether the recent findings merely indicate a recent invasion of the bat population which may spread in succeeding years.

Variants of Rabies Virus

For many centuries, rabies virus has been maintained in nature in canines (wolves, dogs, foxes, and jackals) in a form to which Pasteur gave the name "street virus." When taken into the laboratory and passed serially through rabbits, mice, or other animals, certain changes occur and it then becomes "fixed" for that species, or, in Pasteur's

words, it becomes a "virus fixe'." A "fixed" virus differs from the "street" virus in several important ways: the infective titer of the virus increases; the incubation period becomes shortened and constant; Negri bodies are no longer produced or, if produced, tend to be small and few in number; and infectivity for other species of animals decreases markedly. Different strains of rabies virus vary in their ability to be fixed, some requiring forty to fifty serial transfers in a given species while others may be fixed in one or two transfers. It is not known why the virus, when transmitted in canines in nature, remains a street virus and does not become fixed for these species.

Thus, the rabies virus exists in at least three variant forms, the street virus, the fixed virus, and the bat virus which can probably be looked upon as a variant, since it produces a primarily paralytic disease in infected animals and in man. In this latter regard it more closely resembles the fixed virus. Excellent descriptions of the clinical course of rabies in man and animals can be found in most of the standard textbooks, two of which are listed in the references for this paper.

Source of Infection

Almost all human infections occur as the result of bites from rabid dogs and our present civilization appears to be well able to support the disease indefinitely by means of its stray dog population, especially in the larger cities. In certain areas of the United States, foxes provide a potent reservoir of rabies infection, but their threat to humans is not great. They do cause considerable economic loss by infecting cattle, horses, sheep, and pigs. Occasionally, epidemics of rabies have occurred in skunks, and squirrels and cats are sometimes found infected. At the present time, then, the dog population constitutes the real problem in rabies and its control. If rabies in dogs can be prevented, the disease will, in all probability, be of little consequence in a few years. This, of course, assumes that bat rabies will not prove to be a serious menace.

The number of human cases of rabies in the United States is never very high in any given year, ranging from four to 103 cases per year (1908-1949). Each case represents a death, since the mortality rate is 100%.

Vaccination

There has been available, since the work of Pasteur, a prophylactic vaccine for use in humans and more recently in dogs. The present vaccines are prepared from the brains of infected rabbits. The virus used for infecting the rabbits is a fixed virus derived, in most cases, as an offshoot of the virus strain used originally by Pasteur. Most of the preparations are two to five *per cent* suspensions of the rabbit brain in which the virus has been inactivated, either by the addition of phenol or, more recently, by irradiation with ultra-violet light. The latter appears to yield a better vaccine. The usual course of vaccine for humans consists of fourteen to twenty-one daily inoculations with two to five ml. amounts given subcutaneously. It is fortunate that the incubation period of the disease is usually long enough to allow for intervention with the vaccine after the exposure has occurred.

A certain amount of controversy and misunderstanding exists regarding the efficacy and dangers involved in the use of the Pasteur vaccine. With regard to efficacy, figures are not easy to obtain, but certain studies indicate that definite reductions in the number of cases have resulted from use of the Pasteur treatment. First, it may be cited that in individuals bitten by rabid wolves, seventy-five *per cent* develop rabies if not treated, while only nine *per cent* of those that are vaccinated develop rabies. The high infection rate is probably due to the usual severity of wolf bites. Second, overall figures for all persons bitten by rabid dogs and not treated show that from five to fifteen *per cent* develop rabies, while the incidence of rabies in treated persons is 0.3 to 0.4 *per cent*. In a study reported by Sellers with figures compiled at the Georgia State Health Department, it was shown that the failure rate in persons bitten about the face was 1 in 160;

on the hands, 1 in 1800; on the body, 1 in 4350; and on the feet and legs, 1 in 6670. Over fifty *per cent* of the recorded failures occurred in individuals bitten about the face where the average incubation period was twenty days. As the average incubation period increased, the percentage of failures decreased. Thus, the incubation period for bites about the hands and arms was thirty-three days and for bites on the body and legs and feet it was fifty-nine days. Studies by Koprowski and Cox have also shown that failures occur most frequently in individuals severely bitten about the face and hands. Recent studies indicate that at least some of these failures can be prevented if hyper-immune serum is given within twenty-four to seventy-two hours after the bite has occurred.

Post-Vaccinial Reactions

Pasteur vaccination is not without its dangers, although it is possible that these are somewhat over-emphasized at times. Reactions are of several types. In the first place, the series of inoculations is long and concentrated and the amounts given are such as to cause discomfort. In apparently seventy-five to eighty *per cent* of individuals this discomfort, plus occasional Arthus type reactions, constitutes the extent of the difficulty. In about twenty *per cent* of patients there is an urticaria which clears readily after cessation of the vaccination. Severe reactions in the form of post-vaccinial paralysis occur in about one out of 3000 persons. These range from simple neurosis to encephalomyelitis, and occur either towards the end of the series or within about ten days after the last inoculation. It has been estimated that one death occurs for about every 300,000 persons vaccinated. Fortunately, of those who survive, nearly all recover completely. It has been found that a considerable *per cent* of the severe reactions occur in individuals who are being given the Pasteur treatment for the second or third time. Five of seven cases reported in Georgia since 1925 have been in persons being treated for a second time. Available evidence indicates that reactions to rabies vaccination result from the introduction of large amounts of central nervous system tissue and is an immunological reaction to an organ-specific tissue.

It seems reasonable to conclude from the above figures that the dangers of reaction to the Pasteur vaccine are not great enough to preclude its use, but do make it imperative that the vaccine not be given without due cause.

DIAGNOSIS OF RABIES IN ANIMALS

After a person has been bitten by a dog, it is imperative that certain rules be followed in order to establish the presence or absence of rabies in the animal. The dog must not be killed unless it shows advanced symptoms of the disease. If killed, it must not be hit or shot in the head. In most cases, the dog should be caught and held for observation for a minimum of seven to fifteen days. If clinical signs of rabies develop, the dog should be killed and the head packed in ice and sent to a laboratory for examination. The finding of Negri bodies is diagnostic of rabies and this can easily be accomplished by properly trained personnel. It has been recommended that brain suspension from all doubtful cases be inoculated intracerebrally into Swiss mice. In some laboratories where facilities are available, it is routine to inoculate material from all dogs into mice. In this way, about ten *per cent* more positive results are obtained, but this means a delay of several days and it is not always desirable to wait that long to start human vaccination.

CONTROL OF RABIES

The control of rabies obviously hinges on the dog population at the present time. The methods for accomplishing this are well known and have proven effective in numerous instances. The collection and disposal of stray dogs and vaccination of all pet dogs is sufficient in most cases. The vaccine used for dogs is made in the same manner as the human vaccine, except that it is used in much more concentrated form and given as a single dose. Dogs should be kept

isolated for thirty days after vaccination to allow for immunity to develop. It has been found that three inoculations, given at weekly intervals, are better than one, but the procedure is difficult to carry out in general practice. Reactions to the vaccine occur infrequently in dogs and are not generally serious. It is necessary that dogs be vaccinated yearly.

Recently, a new vaccine has been developed which appears to protect dogs for as much as three years. It is a chick embryo adapted strain of virus which has lost its ability to produce disease in dogs, but has retained its ability to infect and stimulate antibody production and resistance to rabies. Promising results have been reported from the use of this vaccine and it is now available for use in a number of places. No adverse effects from the vaccine have been reported.

As indicated above, local control measures involving collection of stray dogs and vaccination of pets, or the initiation of "quarantine," is effective in a community, but control from such measures can only be temporary, unless all surrounding communities initiate similar measures and unless these measures are continued indefinitely. No matter how large an area is covered by a rabies control program, the fringe areas are always subject to occasional cases due to migration of infected animals from regions not under control. Thus, it is obvious that any permanent rabies control program must be carried out on a national basis. Even with a national program, the borders between nations would have to be supervised very carefully to avoid reintroduction of the disease. England and Australia have been free of rabies for a number of years. This is because control is applied on a national basis and there are no borders with other countries by which the disease can re-enter. No dogs can be brought into England without being vaccinated and held in quarantine for six months.

HANDLING OF PERSONS EXPOSED TO RABIES

Persons exposed to rabid or suspiciously rabid dogs present a problem to physicians and health officers wherever they occur. The following quotation from a paper by Dr. T. E. Sellers, who has had a very long experience with these problems, summarizes the situations and possibilities quite well:

"Out of long observation and tested experience have emerged two important principles: The first of these is that rabies can be naturally transmitted to man only by the direct inoculation of infectious saliva into the flesh deep enough to come in contact with nerve tissue; *e.g.*, wounds made by the teeth of the actively rabid animal. The second concept is that antirabic vaccine prepared from brain tissue may, if repeatedly injected over a long period of time, induce a specific brain tissue sensitization which may precipitate the phenomenon of treatment paralysis, always a serious and often fatal complication.

Local Treatment

"The health officer or clinician should be ever aware of these two principles as he faces the endless variety of problems of human exposure. Most, if not all, of such problems can be disposed of safely to the best interest of all concerned by the application of the following course of procedure:

"*Local Treatment of Wounds*: All animal bites and especially those made by dogs, foxes, and cats, should be washed immediately and thoroughly with strong soap solution, preferably twenty *per cent* tincture of green soap, but any soap will probably suffice. Continue the washing for at least ten minutes, forcing the soap solution repeatedly into all parts and depths of the wounds. This simple procedure is just as effective as the age-old practice of cauterization with nitric acid and has the added advantages of cleansing the wounds without pain, avoiding tissue destruction, and scarring. Also, it is a readily available first aid practice that can be safely and quickly applied in the home. The family physician who does not have the opportunity to see the patient at once can advise this expedient over the telephone. Such immediate local treatment is very important, especially

for severe lacerations about the face and hands.

"The next step is to consider the history of the offending animal and here is where the practitioner needs the help of the Health Department. If the evidence falls within the following categories, the animal should be considered as potentially rabid and infectious:

1. The animal is clinically rabid, even though the post-mortem brain examinations fail to reveal Negri bodies.
2. The brain of the animal shows typical Negri bodies, even though the clinical behavior before death was not suggestive of rabies.
3. The animal disappears after biting, or cannot be definitely identified.
4. Any animal that bites without provocation and is immediately killed should be regarded as suspicious even though the laboratory findings are negative.

Indications for Antirabic Therapy

"Having thus arrived at the conclusion that the animal in question is rabid, or that rabies cannot be ruled out, the next step is to direct attention to the nature of the exposure and the need for antirabic treatment. Such treatment is indicated:

1. When there are visible wounds into or through the bare skin that were known or suspected to have been made by the teeth (or claws) of the animal.
2. When the wounds were inflicted through clothing which was torn by the teeth of the animal.
3. When there is reason to suspect that the wet saliva came in direct contact with fresh, open, or raw pre-existent abrasions.
4. When the person exposed is a small child who has been in direct contact with the animal, but who is too young to give reliable testimony.

"Antirabic treatment is not indicated:

1. When the exposure is limited to contact of the saliva with the unbroken skin anywhere on the body, including the face or mouth.
2. If the saliva came in contact with pre-existent wounds which are known to be more than twenty-four hours old or which are covered with unbroken scabs.
3. If the teeth wounds are made through clothing which is not torn. Such wounds are usually bruises or are due to friction from the cloth.
4. If the exposure is limited to:
   a. Handling or petting of the animal, or of other animals with which the infected animal has been fighting.
   b. Handling of objects contaminated with the saliva.
   c. Drinking the milk of rabid cows or goats.
5. If the bite or scratches are inflicted not less than seven days prior to the detection of visible signs of the disease in the animal.
6. If the biting animal remains normal as long as one week after biting.
7. Before administering treatment, the medical advisor should never fail to question as to previous treatment. Regardless of the elapsing interval since the last treatment, re-immunization should be avoided for borderline exposures, such as superficial wounds of the extremities. Retreatment should be limited, in any case, to a short booster series of five or six injections."

DISCUSSION

Rabies, as pointed out before, is not a serious disease in terms of the number of cases and deaths on a basis comparative with such diseases as tuberculosis, influenza, *etc.* Much of the importance of rabies comes from the *fear* and *apprehension* resulting from its presence in a community. The families of persons bitten by a dog live in anxiety awaiting the outcome of any treatment initiated by the physician, and the physician is faced with the problem of deciding what pro-

cedure should be followed. One has but to be in a community where rabies appears in epidemic form to realize the height of feelings that develop in the population. The dog-lover often contributes to these feelings by objecting to compulsory vaccination of dogs as an encroachment of the inherent legal rights of dog owners.

In any area where rabies exists, individuals who are bitten must be given anti-rabic vaccine and this also contributes much to the importance of the disease. The author investigated the situation in one county with a human population of 350 to 400 thousand over a two-year period during a rabies epidemic. It was estimated that the dog population was 80,000. During that period, over 800 positive dog heads were reported from the county health department. Over 1500 persons were given anti-rabic vaccine. There were no human deaths from rabies, but at least one paralytic accident occurred. Thus, even though there were no deaths from rabies, 1500 people and their families were directly or indirectly affected during this period. This constitutes much of the importance of rabies.

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PROBLEMS IN INTESTINAL OBSTRUCTION*

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Intestinal obstruction presents a diagnostic and therapeutic challenge to both the surgeon and practitioner. The mortality continues to remain high despite the many recent advances in electrolyte balance, intestinal siphonage, caloric requirements, and surgical technique. Orr, Wangensteen, Haden, Coller and many others have contributed monumental stepping-stones which enable us to understand the pathologic physiology of this condition.

DIAGNOSIS

Since intestinal obstruction is a symptom complex and not a disease, it is not enough to make a diagnosis of "just intestinal obstruction." To approach this problem we have devised a plan whereby we can make an earlier and more thorough diagnosis, thus enabling proper therapy to be instituted more rapidly. It is necessary to ask and answer the following four questions to correctly diagnose the condition:

(1) Is this an intestinal obstruction?

(2) Is it strangulated or non-strangulated?

(3) Is the obstruction complete or incomplete?

(4) Is it a large or small bowel obstruction?

The Obstructive Triad

In answer to question number one: "Is this an intestinal obstruction?"; we expect to find the obstructive triad, namely, distention, obstipation, and vomiting. The triad may be present wholly or in part, however, its individual parts call for clarification. Since we have no standard for measuring the distended abdomen, we have decided to utilize the anatomic relationship of the umbilicus to the xiphoid process. We believe that the normal abdomen is scaphoid and not flat, hence the umbilicus is normally placed below the xiphoid. When the umbilicus is on a level with the xiphoid, the abdomen is called *flat*, and when the umbilicus is above the xiphoid, the abdomen is described as being *distended*. Therefore, when the umbilicus is on a level with or above the xiphoid, some pathologic condition exists. When such an abnormally placed umbilicus is found we consider the differential diagnosis of the seven "F's," namely, Fat, Feces, Fluid, Flatus, Fetus, Fibroids and "Ph" antom tumors. In almost every case one of the "F's" was found to be the underlying cause. It is important to record the position of the umbilicus when the patient enters the hospital, and to re-check this every hour thereafter. If the umbilicus is below the xiphoid when the patient is first seen, and one hour later is found on a level with the xiphoid, this signifies early distention. In this way we can avoid the development of a late preterminal distention that so many neglected intestinal obstructions present. Regarding *obstipation*, we know that the average intestinal obstruction passes neither feces nor flatus, but we also recall that this may be lacking in incomplete obstruction, as for example in Richter's hernia, in which only part of the circumference of the bowel is incarcerated. In such cases the resulting irritation and hyperperistalsis may even lead to a diarrhea which can be most misleading when one makes a diagnosis of intestinal obstruction. *Vomiting* will be more thoroughly discussed under question number four. Regardless of the absence or presence of the obstructive triad, it is far more important to elicit the one pathognomonic finding of intestinal obstruction, namely, that *pain and intestinal sounds appear at the same time*. This synchronization of sound with

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pain differentiates intestinal colic from any other type of intermittent pain. The physician should place his stethoscope upon the patient's abdomen when he states that he is getting his pain, and if it is of an intestinal nature he will hear the rushing bowel sounds at this time.

Localized Tenderness Suggests Strangulation

Question number two: "Is this a strangulated or non-strangulated intestinal obstruction?" can usually be answered by the presence or absence of *tenderness.* Patients with intestinal obstruction do complain of colicky pain, but the strangulated lesion has pain plus localized tenderness, which is best found by the patient, who will usually locate the exact point of the pathology. The classical example of this is a strangulated inguinal hernia. The patient has diffuse pain over his entire abdomen, but will permit one to palpate it; however, he resents having pressure made over a strangulated mass because of its exquisite tenderness. Our incision is usually determined by the location of the patient's tenderness. Another differentiating point between the strangulated and the non-strangulated obstruction is the appearance of the patient. A patient who has a strangulated intestinal obstruction is acutely and violently ill and usually is in shock, or impending shock, whereas the patient with an intestinal obstruction without strangulation does not present such a dramatic picture. The flat roentgenogram may aid in the differentiation of a strangulated from a non-strangulated small bowel obstruction. If a small bowel, non-strangulated, intestinal obstruction is present, the typical step-ladder pattern is observed and the *valvulae conniventes* are readily seen. If, on the other hand, a small bowel strangulated obstruction is present, no characteristic bowel pattern is assumed since the distended loops arrange themselves in whatever portion of the abdomen the obstruction occurs. The *valvulae conniventes* are not easily detected or seen because of the extravasation of blood into the strangulated loop of bowel and into the abdominal cavity.

Complete Versus Incomplete Obstruction

Question number three states: "Is this a complete or incomplete obstruction?" As has been mentioned, a patient with a complete intestinal obstruction passes neither flatus nor feces per rectum, but if the obstruction is incomplete some flatus and feces may be expelled, especially with repeated enemas. It is important not to be misled by the results of the first enema, since a copious movement and flatus may be expelled following its administration. This, however, is material which is distal to the lesion. If repeated enemas bring flatus and feces, then we assume that the lesion is incomplete; if the returns of the repeated washings are clear, we conclude that the obstruction is a complete one. A "scout" film of the abdomen should be taken when the patient arrives. This immediately reveals the bowel pattern and also determines whether or not flatus is present in the region of the hollow of the sacrum. If the flatus over the sacrum is absent following repeated enemas, we consider the condition a complete obstruction, but if flatus continues to come down and appear over the sacral region, the lesion is an incomplete one. A patient with a complete obstruction will appear more ill than one with an incomplete lesion. Therefore, the clinical appearance and impression is of importance.

Vomiting a Criterion of Location

Question number four, namely, "Is this a large or small bowel obstruction?" The most important differentiating factor in this question is whether vomiting is present or absent. Patients with large bowel obstructions do not vomit, but those with small bowel obstructions do. We all have seen late cases of large bowel obstructions where vomiting has been present as a late and not too distressing symptom, but in the small bowel lesions vomiting appears very early. The higher the obstruction the more fulminant the vomiting. Utilizing this one fact, we can usually differentiate the small from the large bowel ob-

structions. To use the word "fecal" vomiting as being descriptive of intestinal obstruction is incorrect. The term "feculent" is more descriptive, since fecal vomiting refers to a gastrocolic fistula or some similar lesion. The flat roentgenogram is used to further differentiate the small from the large bowel obstruction. It is unnecessary to stand or turn the patient or to give him any contrast media. A flat roentgenogram which can be taken with a portable machine will usually give the desired information. If the obstruction is a large bowel lesion, the roentgenogram usually reveals a large distended colon which appears as a horse-shoe or inverted "U." The rectosigmoid is the most common location for these lesions. If, on the other hand, the obstruction is small bowel in nature, the typical paralleling or step-ladder pattern will be present. The history also aids in differentiating the two types of obstructions. A slow, progressive, chronic, increasing constipation speaks for a large bowel lesion, but a sudden violent attack signifies small bowel pathology.

Patients with intestinal obstruction who have had previous surgery are small bowel obstructions until proven otherwise. The large bowel obstruction resulting from postoperative adhesions is a rarity. A two-quart diagnostic enema is also a help. The large bowel can usually retain two quarts of fluid plus its usual contents. If the bowel cannot take the two quarts, this speaks for a large bowel lesion.

One may make a proper diagnosis instead of just "intestinal obstruction" by using these four questions. The case, therefore, may be diagnosed as a large bowel, non-strangulated, incomplete intestinal obstruction, or a strangulated, small bowel, complete intestinal obstruction, depending upon the findings.

TREATMENT

We have devised a simple plan for the treatment of intestinal obstruction based on the six "S's": Suction, Saline, Sanguine, Surgery, Sulfa, and the "Stir-'em" technic.

Suction, or gastro-intestinal siphonage, has done much to lower the mortality of this condition. It has its pitfalls, however, and these must be kept in mind. It has no place in large bowel obstructions, nor should it be used when strangulation is present. On the other hand, it may be curative in postoperative ileus, non-strangulated adhesive obstruction, or in obstruction associated with peritonitis; these are usually small bowel lesions. Its value as a pre- or postoperative adjunct needs no emphasis. To keep a patient with a carcinoma of the rectosigmoid and a large bowel intestinal obstruction on continuous siphonage is to court disaster.

Saline, an excellent form of supportive therapy, can prolong the life of a patient with an intestinal obstruction, however, it cannot cure the condition. Chloride ions have been lost in the patient who has manifested a great deal of vomiting or in whom continuous gastro-intestinal siphonage has been instituted. These must be replaced, and it is mainly by the use of physiological saline that the patient's chloride balance may be maintained. By restoring this electrolyte balance one is able to put his patient into better condition to withstand surgery, and in this way also to lower the mortality. Saline, however, is not the only supportive therapy that the patient needs; this will be discussed subsequently.

Sanguine is used to refer to blood and its derivatives. We feel that the only place for the use of whole blood is in the replacement of lost red cells. We prefer to keep the protein balance of the patient normal with plasma, serum, or amino acid therapy. If the obstruction is associated with blood loss, we feel that the fluid of choice is then whole blood. In many cases of strangulated obstructions, or in cases which might necessitate extensive bowel resection, whole blood is preferred. Maintaining a normal protein level permits a patient to properly seal because of his good fibrin content. Hypoproteinemia and hyperchloremia are two conditions which must be avoided in the case of intestinal obstruction as well as in all other sur-

gical emergencies. Too little protein and too much chloride both produce tissue edema and permit the patient to "drown" in his own body juices. It is because of hypoproteinemia and hyperchloremia that sutures pull out of edematous tissue. Faulty suturing material is not the cause of intestinal leakage; this is due to poor pre- and postoperative care. The patient's vitamin needs must be maintained, especially the water soluble vitamins B and C which he loses readily. Vitamin C is truly the "surgeon's" vitamin because this is the one which is essential to sound wound healing.

Definitive Therapy

If a patient has a strangulation he should have immediate *surgery.* As has been stated, the patient will tell us where to make the incision if we permit him to reveal his most tender spot. Complete large bowel, non-strangulated lesions require immediate colostomy for the release of intracolonic pressure. We prefer the so-called "blind" cecostomy in such conditions. This is made through an exaggerated McBurney's incision which hugs the anterior superior iliac spine. If the cecum is distended, and it surely should be in an obstructed colon, then it bulges into the wound. It is held in place by two hemostats and an iodoform pack is placed between the cecum and the parietal peritoneum. Following this stitchless procedure, the patient is returned to bed and the cecum is opened some six hours later after it has had a chance to seal off. Since the bowel wall is edematous and will not retain sutures it is unwise to directly attack an obstructed colon lesion. It is for this reason that we leave the primary pathology alone and do a preliminary cecostomy away from the site of the lesion. For the following ten days or two weeks the patient may be deflated, prepared, and then re-operated. It is at this time that a true evaluation of the pathology can be made and a resection done. The cecostomy acts as a vent in the event that intestinal anastomosis is performed. In strangulated lesions we may be confronted with the question: "Is the bowel which has been freed viable or not?" It seems impractical to stand about placing hot towels on a segment of intestine and watch its color. Viability is readily determined if one merely flicks the bowel with the finger and watches for peristaltic waves. If it is able to contract, regardless of the color of the intestine, it is viable. Intestinal obstruction is usually associated with a transudate which is present in the peritoneal cavity; if this is bloody a strangulation is present. Therefore, if a blind cecostomy is done and a sanguinous fluid noted, we must abandon the cecostomy and explore for the presence of a strangulated lesion. The type of anastomosis performed is purely a personal one, however, we feel that a lateral anastomosis is the safest in the hands of the occasional operator. If time is a factor, one should be familiar with the technic of the so-called quick "aseptic" end to end anastomosis.

Sulfa drugs have taken their place among the chemotherapeutic agents used in the treatment of intestinal obstruction. There is also a place for such allied drugs as penicillin and streptomycin. Our routine is to give 600,000 units of Penicillin twice a day and one gram of Streptomycin every six hours for the first day and one-half gram every six hours for three days thereafter.

By *"stir-'em" technic* we mean early ambulation, active and passive movements, and breathing exercises. The beneficial effects brought about by getting the patients out of bed as soon as possible have been well proven. We do not wish to infer that early ambulation should be carried to an extreme. It is our plan to have our major surgical cases out of bed on the first postoperative day, however, each case presents an individual problem. Having the patient move about, having him take a few deep breaths every hour, and encouraging arm and leg movements all

play their part in lowering the incidence of phlebothrombosis, pulmonary complications, and their sequelae.

In this discussion of the subject of intestinal obstruction, only the highlights have been mentioned, however, we feel that if we approach the problem with the "Four Questions," make a diagnosis based upon these, and then summarize the treatment with our "Six S's," we should have a logical approach to a given case.

THE EXPERIMENTAL STUDY OF TUMORS IN THE CENTRAL NERVOUS SYSTEM — A Review*

ULRICO SACCHI, M. D.** and RENATO BASERGA, M. D.***

The experimental study of tumors of the nervous system and its mesenchymal sheaths can be studied in three different ways, namely, with the occurrence of spontaneous tumors in animals, the induction of tumors by carcinogenic substances, and the transplantation of tumors.

Spontaneous tumors of the nervous system in animals are quite rare in the literature, though probably they are not as rare as the paucity of reports would suggest. It is reasonable to believe that tumors of the nervous system are often overlooked by research workers, dissection of the central nervous system being very seldom included in the routine autopsy procedure. However, various types of brain tumors have been described in domestic animals, such as dogs[1,2,3], cats[1], horses[1], and fowl[1,4]. On the other hand, spontaneous brain tumors appear to be exceedingly rare in laboratory rodents; apparently the only instance recorded in the literature was a "cellular endothelioma" of the cerebrum reported by Slye, Holmes, and Wells[5] during their examination of over 11,000 brains of mice. The occurrence of a spontaneous pinealoma in a silver fox, reported by Schlotthauer and Kernohan[2], may be mentioned here. Tumors of nerve-sheaths are apparently more frequent than brain tumors in animals. A disease comparable with human neurofibromatosis has been described in the horse, dog, deer[6], and ox[7]. Nerve sheath fibromas in a family of brook-trout have been reported by Young and Olafson[8], while Lucke[9] records seventy-six instances of typical neurilemmomas in adult fish belonging to the species of snappers.

Local Application of Carcinogens

The induction of brain tumors by means of carcinogenic substances constitutes one of the most recent chapters of experimental oncology. The first positive result was reported in 1936 by Oberling, Guerin, and Guerin[10], by local application of benzpyrene, and these results were confirmed a year later by Askanazy[11]. In both series of experiments, however, only a single positive finding was recorded. A much better method, yielding a higher incidence of positive results, was described in 1939 by Seligman and Shear[12]. Using C3H mice and methylcholanthrene by local application, they obtained eleven gliomas and two fibrosarcomas. These tumors were transplantable in the subcutaneous tissues of mice of the same strain. Similar results were obtained by Peers[13] using cholesterol pellets containing ten *per cent* methylcholanthrene. The implantation of such pellets in the central nervous system produced seventeen sarcomas and fifteen gliomas in eighty-seven Swiss mice. A particularly careful study of experimental brain tumors was reported by Zimmerman and Arnold[14]. These authors used C3H mice and methylcholanthrene, the carcinogen being implanted in three different sites—the cerebrum, cerebellum, and meninges. Out of a total of 103 mice, they were able to obtain forty-eight intracranial tumors, the percentage of positive results being about the same in all three locations (Table I). However, when the carcinogen was implanted into the cerebrum, glioblastomas were the predominating tumors, while

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TABLE I

(Zimmerman and Arnold)

Incidence of brain tumors induced with methylcholanthrene according to site of pellet implantation.

	Group I (Cerebrum)	Group II (Cerebellum)	Group III (Meniges)
Total number of animals	57	30	16
Negative for tumor	31	17	7
Total number of tumors	26	13	9
Unclassified tumor	1	2	—
Gliomas	15	8	2
Astrocytoma	1	—	—
Glioblastoma multiforme	4	2	—
Medulloblastoma	1	3	—
Oligodendroglioma	3	—	—
Spongioblastoma polare	—	—	1
Unclassifed glioma	5	3	1
Multiple gliomas	1	—	—
Sarcomas	5	1	7
Rhabdomyosarcoma	2	—	6
Meningeal sarcoma	2	—	1
Cerebral sarcoma	1	—	—
Mixed sarcoma and glioma	5	2	—

medulloblastomas were more frequent in the cerebellum, and sarcomatous tumors in the meninges. Such distribution is similar to that of the different histological types of tumors in the human central nervous system. The tumors produced by Zimmerman and Arnold were also transplantable in the subcutaneous tissue of homologous strain mice.

The use of dibenzanthracene as a carcinogenic agent gave contradictory results by the local application of the carcinogen, while Arnold and Zimmerman[17], with the same technique, but using C3H mice, obtained five intracranial tumors in twenty-one animals.

Oral Carcinogens

In all these experiments, which were confirmed in many other instances[30,31, 32,33,34,35], the carcinogen was used by local application, but undoubtedly the production of brain tumors by feeding a carcinogenic substance is of greater significance. This could be achieved by feeding rats with acetylaminofluorene, a substance which has been demonstrated to be carcinogenic on various organs. By this method, a glioblastoma was obtained by Vaquez-Lopez[18], while Hoch-Ligeti[19] produced two glioblastomas in thirty animals fed with acetylaminofluorene. These results open an interesting approach to the study of environmental brain tumors.

Transplantation Studies

Transplantation studies on experimental brain tumors can be subdivided into two groups: studies on the transplantability of induced brain tumors and studies on the transplantability of heterologous tumors into the brain substance. As we mentioned above, induced brain tumors are transplantable into the subcutaneous tissue of mice of homologous strains[12,14]. When mice of alien genetic constitution are used, the tumors do not take in the subcutaneous tissue, but usually grow if implanted into the brain substance or the anterior eye chamber[20]. According to Shirai[22], Murphy and Sturm[23], and Greene[21], transplantation into the brain substance permits a successful growth of heterologous tumors, namely, tumors originating in animals of different species and even human tumors.

Applications to Human Pathology

Some of the findings reported above can be successfully applied in human pathology for a better understanding of the tumors of the nervous system and its

mesenchymal sheaths. In the first place, the possibility of inducing brain tumors by feeding the animals with a carcinogenic substance must be emphasized[18,19].

The etiology of spontaneous brain tumors has always been considered obscure. The most widely accepted theory is that gliomas are the result of an embryogenic disturbance in the structure of the nervous system. Von Rindfleisch[24] assumed the existence of superfluous embryonal tissue distributed in the glia-structures as the source of the cells of origin of gliomas. The medulloblastoma is presumed to arise from the germinal cells in the flocculonodular lobe of the cerebellum[25]. In some cases brain tumors have been found to be related in their clinical appearance to trauma. There is no evidence, however, that a causal relationship exists[26]. The demonstration that brain tumors can be induced by local application of a carcinogenic substance has already pointed out the possibility that such tumors might arise outside of a developmental disturbance.

Methylcholanthrene-induced tumors indicate that the brain tissue is responsive to chemical carcinogens in the same fashion as other tissues. The demonstration that such tumors can be produced by indirect action, namely, by feeding a carcinogen, is a further step which raises the problem of environmental causes in the etiology of human brain tumors. Undoubtedly, other factors must be involved in the induction of experimental brain tumors, as demonstrated by the low percentage of positive results. Hereditary factors are certainly involved, as is shown by the fact that C3H mice are responsive to the carcinogenic action of dibenzanthracene, while Swiss mice are unresponsive. However, the possibility that brain tumors may be produced by external agents of chemical nature cannot be discussed until the problem has been well investigated in human pathology.

Metastasis of CNS Tumors

Another important conclusion which can be drawn from the above-mentioned results concerns the problem of metastases. It is well known that tumors of the central nervous system usually do not metastasize. The possibility of transplanting induced brain tumors into the subcutaneous tissue of animals of the same species suggests that tumor cells of nervous tissue origin are viable outside of the central nervous system. The rarity of metastases seems, therefore, to be due to anatomo-functional factors rather than to the incapacity of brain tumor cells to grow outside of the nervous tissue. It is also interesting to notice that, according to Zimmerman and Arnold[14], serial passages in the subcutaneous tissue of induced brain tumors purifies the tumors. For example, a glioma which could not be classified originally assumed the typical appearance of a glioblastoma multiforme after serial passages in the subcutaneous tissue, while the mesodermal component of the original tumor was gradually lost during the passages. If we keep in mind that, according to Greene[21], malignant human tumors grow when transplanted into the brain substance of the guinea pig, it is reasonable to believe that the method of serial passages into the subcutaneous tissue may be of some help to the pathologist, in an attempt to classify some spontaneous tumors which occur in human pathology and which cannot be easily recognized at their primary site. The use of *in vitro* cultures of brain tumor cells has also been suggested by some authors[27,28,29] in a similar attempt to facilitate the diagnosis by the pathologist; in such cases the use of jelly-foam as a substrate has been particularly recommended.

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CLINICOPATHOLOGIC CONFERENCE

Presented at Mount Sinai Hospital, Chicago, Illinois

DR. L. EDIDIN, Chairman DR. I. DAVIDSOHN, Secretary

Abstracted by DR. I. KACIONIS

Clinical History

First admission: The patient, a sixty-seven year old white female, entered Mount Sinai Hospital for the first time on October 17, 1950, because of a bulging vaginal mass which had been troubling her for two years. In addition, she had stress incontinence and severe constipation. However, she had never noted any vaginal bleeding or spotting. Menopause had occurred thirteen years before. The patient had been diabetic "for a long time." Past history also revealed that the patient had an appendectomy twenty-five years before and ophthalmic surgery four months before.

Physical examination revealed a well-developed, obese, white female in no acute distress. The blood pressure was 180/120; the pulse rate was seventy-six and regular. There was a pterygium of the left eye. The lungs were clear to percussion and auscultation. Examination of the heart and abdomen was negative. The lower extremities had bilateral varicosities. On pelvic examination there was a large rectocele and cystocele and a small urethrocele. The uterus was atrophic. The adnexae were negative.

On October 25, 1950, a vaginal and rectal plastic operation was performed. The patient made an uneventful recovery and was discharged on November 5, 1950.

Second admission of the patient was on December 13, 1952, at which time she complained of weakness, lethargy, anorexia, and low back pain of two weeks duration. These symptoms were so marked that for one week prior to admission she had been bedridden. There was no history of nausea or vomiting. Nocturia (seven to eight times) had been present "for months."

Physical examination revealed a semi-stuporous female with Kussmaul breathing. The skin and mucous membranes were very dry and warm. The chest was emphysematous. There was dullness in the right lower lung field associated with numerous fine rales. Dry wheezes were heard over both lung fields. There was a grade two systolic murmur at the apex. The blood pressure was 190/100; the pulse rate was 100 and regular. Examination of the abdomen and extremities was negative.

The impression on admission was diabetic coma or a cardiovascular accident with encephalomalacia. The patient deteriorated rapidly during her hospital stay, developing bronchopneumonia two days later. Despite daily treatment with Terramycin, Dicrysticin, and digitoxin the patient expired on December 17, 1952, four days after admission.

*Dr. Harry J. Isaacs**: The electrocardiogram taken on first admission was normal. The second, taken two years later, showed some abnormalities. We tried to interpret it with relation to the diabetic condition. Acute coronary thrombosis is a common occurrence in a female with diabetes and hypertension, but in the electrocardiogram there was no expression or evidence of an acute myocardial infarct. Secondly, chronic coronary disease or sclerosis is also found frequently in such cases, but there was no evidence of that. Thirdly, with a patient in coma, we had to consider the possibility of electrolyte imbalance, but in the electrocardiogram there was no suggestion of potassium or calcium disturbance. The only positive findings were a depression of the S-T segments interpreted as a digitalis effect, and some abnormality with a little widening of the QRS complex. As a terminal event in

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LABORATORY DATA

First Admission

Blood counts:	RBC (mill.)	Hb. (Gm.)	C.I.	WBC	Differential Count (in %) Segs	Eos	Bas	Lymphs	Monos
10/18/50	4.7	14.8	1.01	5750	41	1	1	51	6

Blood chem:	Sugar (mg/100 cc.)	Urea N	A/G	T.P. (Gm.)	Alb. (Gm.)	Glob. (Gm.)
10/18/50	210	10.4	1.9	7.6	4.9	2.7
10/20/50	220					
10/23/50	271					
10/26/50	335					
10/27/50	275					
10/30/50	195					
10/31/50	120					
11/3/50	237					
11/6/50	275					

Urinalyses:	Color	Sp.Gr.	Alb.	Sugar	React.	WBC	RBC	Epith.	Chem. Blood	Acet.
10/18/50	Amber	1.020	0	0	6.0	1-2	-	rare	0	
10/24/50	Yellow	1.017	Tr.	0.4%	5.5	4-6				
10/26/50	Yellow	1.021	Tr.	2.3%	5.5	2-3		rare		
					(Casts: 4-6 hyal. and some gran.)					
10/27/50				1.0%						Mod.
10/28/50				0						0
10/30/50				1.0%						Tr.
11/1/50-7 AM				2.4%						0
11/1/50-11 AM				2.0%						0
11/1/50-3 PM				1.5%						0
11/2/50-7 AM			Tr.	0.8%						0
11/2/50-3 PM				1.0%						0
11/3/50-7 AM				0.4%						0
11/3/50-3 PM				0.3%						0
11/3/50-7 PM				0.4%						0
11/3/50-12 PM				0.5%						0
11/4/50-7 AM				0						0
11/4/50-11 AM				0						0
11/6/50-7 AM				0						0

Serologic tests for syphilis: 10/18/50-Kahn, Wassermann, Kline: Negative.

ECG: 10/18/50 - Normal.

Second Admission

Blood counts:	RBC (mill.)	Hb. (Gm.)	C.I.	WBC	Differential Count (in %) Segs	Eos	Bas	Lymphs	Monos	Stabs
12/15/52	2.98	9.2	1.0	5500	61	-	-	27	4	8
	(2 Nucl. RBC/100 WBC. Anisocytosis 2+; Bas. stippling-rare)									
12/16/52	3.14	10.15	1.0	4500	32	-	-	15	3	36
	(Reticulocytes 1.8%; Platelets 163,000-control 286,000)									
	(Myelo 2; Meta 14; Macros 1+; Polychromatophilia 1+)									
	(2 Nucl. RBC/100 WBC. Doehle bodies +++)									

Blood chem:	Sugar (mg/100 cc.)	Urea N	Creat.	Na	K (mEq/L)	Cl	CO_2 C.P. (mM/L)
12/13/52	95						7.6
12/14/52	72	117					16.6
12/15/52	70	98.6	6.7	141	5.0	107.1	12.2

Urinalyses:	Color	Sp.Gr.	Sugar	React.	WBC	RBC	Epith.	Acet.	Prot.	Casts
12/13/52			0					0		
12/15/52	Amb. cldy.	1.014	0	5.5	1-2	0	Occ.	0	2+	0
12/16/52	Amb. cldy.	1.012	0	5.5	rare	0	rare	0	2+	0

Serologic tests for syphilis: 12/17/52 Kahn, Wassermann, Kline: Negative

ECG: 12/16/52 - Abnormal

Blood culture: 12/23/52 E. coli; Hemolytic staph. aureus; Gamma Strep.

Figure 1

Figure 2

uremia there is occasionally some pericardial involvement, but no evidence of this was manifested by the electrocardiogram.

In summary, there was no electrolyte disturbance or evidence of acute or chronic coronary disease. There was some expression of digitalis effect and there were some nonspecific abnormalities which might be attributed to left heart strain.

Dr. P. Silverio:* X-ray examination of the chest performed in December, 1950, disclosed emphysema of the upper lung field, accentuation of the hilar shadows and prominence of the basal bronchovascular markings, especially on the right side. This may be interpreted as bronchiectasis or interstitial fibrosis. In the heart, we noticed some enlargement, particularly of the left ventricular segment. Examination of the chest performed seven days later disclosed no gross changes. Examination of the lumbosacral vertebrae (Figures 1 and 2) performed two years later showed severe osteoporosis with collapse of the vertebrae, some vertebral lipping, widening of the intervertebral spaces, and softening of the vertebral bodies. There was marked calcification of the abdominal aorta.

Clinical Discussion

Dr. Donald Atlas:** In considering the demise of one who was a diabetic for many years, the mode of death is an interesting problem. Patients with diabetes and hypertension are common at Mount Sinai Hospital and they may die in one of several ways: a cerebrovascular accident, coronary thrombosis, diabetic acidosis, infection (bronchopneumonia), or a renal complication. When this patient was admitted for the second time she was in a state of coma and did not respond at all. She also had some weakness of one facial nerve and we therefore suspected a cerebral hemorrhage. The spinal puncture was entirely negative, but this did not completely exclude the diagnosis of a cerebral thrombosis or a massive brain hemorrhage which had not as yet eroded into the subarachnoid space. Since she was diabetic, her metabolic state had to be assessed, and from laboratory reports it is obvious that the patient was not in diabetic acidosis. In fact, there was comparatively little sugar in her urine. She

*Resident in Radiology, Mount Sinai Hospital.

** Associate Attending, Mount Sinai Hospital; Associate Professor of Medicine, The Chicago Medical School.

was acidotic, but not to a degree sufficient to produce coma, because it takes a very intense acidosis with a marked depression of the CO_2 combining power and a marked increase in hydrogen ion concentration to produce acidotic coma. This diabetic was not in diabetic acidosis.

There also remains the likelihood of the renal complications of diabetes and hypertension. There are three or four renal complications of diabetes. The most frequent, in our experience, is pyelonephritis. The urinalyses, however, were entirely negative; there was very little pus and there were no casts or blood cells in the urine. Nevertheless, a diabetic can have pyelonephritis for many years with pus and red cells in the urine in the early stages, while later the urine becomes strangely clear. The end-result of this pyelonephritis becomes manifest as hypertension with renal insufficiency. In favor of pyelonephritis is the fact that on a previous admission she had gynecological surgery — repair of a cystocele and a rectocele. At that time there were hyaline and granular casts in the urine and very few white cells. Pelvic surgery and long-standing cystocele may have in some measure contributed to a pyelonephritis.

Another renal complication of diabetes is intercapillary glomerulosclerosis. This is actually a pathologic diagnosis and cannot be made with certainty at the bedside, although the syndrome has been described as consisting of azotemia, edema, hypertension, and albuminuria. There was no edema and little albuminuria in this case, but there was azotemia. Clinically, there were few grounds upon which to make a diagnosis of Kimmelstiel-Wilson syndrome.

A third and more infrequent complication of diabetes, but the condition which I thought this patient had at the time, is hemorrhagic necrosis of the pyramids of the renal papillae. This is an acute fulminating disease, usually associated with numerous casts and pus in the urine, pain in the back, high fever, and a rapid downhill course. This patient had a rapid downhill course, but the urine was rather clear for the patient to have had hemorrhagic pyelonephritis.

Diabetics of long standing are susceptible to arterio- and arteriolosclerosis and the kidneys of diabetics often show advanced arteriosclerotic changes. I feel that the uremic state in this patient was due to a degenerative renal disease — arteriosclerosis and arteriolosclerosis — but it is impossible to make that diagnosis with certainty.

This patient had either a cerebral hemorrhage which we could not establish clinically (it did not rupture into the subarachnoid space), giving her a secondary extra-renal azotemia, or she had some primary renal disease complicating her diabetes. She probably had the latter, but which of the two it is difficult to say because of the absence of urinary findings. The chances are that she had a pyelonephritis, although my diagnosis at the bedside when I first saw her was a hemorrhagic papillitis, a necrotizing papillitis, in spite of the absence of urinary findings.

Just before her death her serum chloride and sodium were normal, and the CO_2 combining power was only moderately depressed. Certainly electrolyte imbalance was not the cause of her death.

*Dr. Milton Tinsley:** The diagnosis of a possible cerebral affair brings me here to discuss this case. The presumptive diagnosis of a cerebral hemorrhage seems to be a prominent one. If the patient had a cerebral hemorrhage there would be an increase of the intracranial pressure. Blood in the spinal fluid is not always found in these conditions. However, there frequently is increased protein in the spinal fluid. This patient had a progressive coma preceded by lethargy and back pain. This suggests a progressive lesion, since hemorrhage would produce a sudden onset of symptoms and signs. A progressive condition beginning with pain in the back would be more likely to indicate a diagnosis of tumor or abscess. Encephalomalacia would provide more prominent neurological findings, perhaps without any increased spinal fluid pressure.

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* Attending Neurosurgeon, Mount Sinai Hospital; Associate Professor of Neurosurgery, The Chicago Medical School.

I should like to take this opportunity to emphasize a few important points in the performance of a spinal puncture. First, a spinal puncture should never be performed unless a manometer is available. If the suspected lesion is intracranial, the Queckenstedt maneuver should not be performed. It will not give any pertinent information and may be dangerous. However, if an intraspinal lesion is suspected, a Queckenstedt maneuver should always be done. In performing the Queckenstedt maneuver, both jugular veins should be compressed. Unilateral jugular compression is of no value unless a lateral sinus thrombosis is suspected. I feel that the most likely diagnosis here is a tumor.

Dr. D. Atlas: This woman had a complete neurological examination and the only objective sign was unilateral facial weakness. The spinal puncture was done by the resident and he told me at the time that the pressure was normal, the fluid clear, and the Pandy negative. This indicated a normal protein content. A culture was also made. A diagnosis of vascular disease of the brain was made on the basis of probability. For every brain tumor in a sixty-seven year old diabetic, a hundred such patients will have a cerebrovascular degenerative lesion of the brain. That, of course, does not mean that one should ignore the possibility of neoplasms of the brain in every patient who comes in with an obvious cerebrovascular accident.

In explaining the amelioration of the diabetes as the patient deteriorated clinically, one should recall that it is not uncommon to see elderly diabetics show a false improvement. That is, the threshold for sugar may rise as renal insufficiency supervenes; consequently, the urinary sugar progressively diminishes. Thus it is easy to understand that patients may have blood sugars 300 mg./100 cc. or greater without glycosuria. I am sure Dr. Weisberg will concur. In renal disease, generally, the more one finds in the urine the better is the patient, and quite often the better the urine, the worse the patient. It is not unusual to see a patient in terminal azotemia due to chronic glomerulonephritis who has an absolutely clear urine, because as the renal blood flow is decreased, the filtration fraction is also decreased. Less and less of the formed elements filter into the urine. The urine is curiously clear, and thus unreliable for the diagnosis of advanced renal insufficiency.

Question: How do you account for complete disappearance of diabetic symptoms?

Dr. D. Atlas: I have no answer for that. Perhaps Dr. Weisberg has.

The positive blood culture was merely a terminal phenomenon, for as far as I remember it was not done early. I think the report on this blood culture probably arrived after the death of the patient and I do not consider that it had any bearing upon the case.

Question: What are the Doehle bodies referred to in the blood count on December 16, 1952?

Dr. I. Gore:* Doehle bodies are blue-staining granulations observed in the polymorphonuclear cells. They are most frequently seen in the exanthemata of childhood. They occur characteristically in Scarlet Fever, but not in German Measles. Not much is known about their nature but some people consider them to be hypertrophied toxic granules, while others have different ideas. I have had no personal experience with them.

Dr. H. J. Pilka:** Terminally, this patient had a normal blood sugar, so that the theory of Dr. Atlas does not apply here. I wonder if a possible tumor of the pancreas might produce hyperinsulism (tumor of the pancreas with metastases) and thus, the diabetes would be offset. Also, there is no explanation of the apparent blood dyscrasia or of the myelocytosis and metamyelocytosis.

Dr. H. J. Isaacs: In this case, where there is supposedly some cerebral pathology, it is of interest to recall the Hous-

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* Pathologist, Mount Sinai Hospital; Associate Professor of Pathology, The Chicago Medical School.

** Clinical Assistant in Surgery, Mount Sinai Hospital.

say phenomenon. When the pituitary is removed from a diabetic, the diabetes clears up. Thus, in a case with an intracranial lesion, metastatic or primary in character, malignant or otherwise, with destruction of the pituitary gland, the diabetic condition improves considerably. Is that a possibility in this particular case?

*Dr. A. J. Levine:** When I observed the osteoporosis, collapse of the vertebrae, and renal findings with only a two plus albuminuria, I thought the possibility of a multiple myeloma should be considered. The absence of hyperglobulinemia, in this case, does not preclude such a diagnosis. The occurrence of an anemia between the first and second admissions, the X-ray findings, the renal findings, and the possibility that this patient died in uremia, suggest that the primary cause might be multiple myeloma.

Dr. D. Atlas: I have not seen a myeloma producing azotemia with so little in the urine. When myeloma involves the kidney it does so in one of two ways: either by precipitation of protein casts obstructing the nephrons, or by infiltration of the renal parenchyma with amyloid. In either instance, one would expect to find more in the urine than was found in this case. I should say that myeloma in such a case as this is very rare.

Dr. A. J. Levine: The low red count, the low hemoglobin, and the normocytic anemia are a reflection of azotemia. The interrelationship of anemia and azotemia has not been explained, but there has been some recent work upon that subject. As to the question of the myeloma producing no hyperglobulinemia and only a two plus albuminuria; it has been shown, especially by Meacham, that patients with Bence-Jones protein in the urine and elevated ionized calcium in the blood may have renal changes, most likely in the nature of casts in the tubules. These cases usually do not show hyperglobulinemia.

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Clinical Diagnosis

1. Diabetes Mellitus
2. Uremia—secondary to degenerative renal disease
3. ? Pyelonephritis
4. Cerebrovascular disease
5. Bronchopneumonia

Pathologic Diagnosis

1. Bronchopneumonia
2. Cardiac hypertrophy and minimal para-amyloid infiltration
3. Coronary vessel sclerosis
4. Mitral valvular calcification and ossification-myelomatous infiltration
5. Passive congestion of the liver with toxic fatty degeneration
6. Renal arteriosclerosis and tubular myeloma casts
7. Osteoporosis of the vertebrae with myelomatous infiltration

Autopsy Findings

Dr. Ira Gore: The gross autopsy findings did not reveal the cause of the coma. On examination of the brain, it was found to be quite normal for the patient's age. There was moderate sclerosis of the basal vessels but no parenchymal lesions were found. The lungs were moderately increased in weight and showed a patchy pneumonic process in the lower lobes and a moderate degree of pulmonary edema. The heart was moderately enlarged (410 Gm.) for a small woman and there was moderate sclerosis of the coronary vessels. There was a slight stenosis of the mitral valve involving only the anterior leaflet and grossly the myocardium felt quite firm. The liver showed only congestion. The spleen was of average size. The kidneys grossly were of average size and there were a few indented, pitted scars that we see frequently in elderly patients. We attribute this to arteriosclerosis. The kidney structure showed some pallor with well-preserved cortical markings and cortico-medullary distinction.

On the basis of the gross examination we could not shed much light on the problem, but microscopically we have the answer. The vertebrae were quite

porotic, as the X-rays had revealed, and there was diffuse replacement of the normal hemopoietic marrow by plasma cells (Figure 3). Practically all the cells seen are myeloma cells. On the basis of this displacement of the normal blood forming tissue, it is quite easy to understand the mechanism of this patient's anemia. Clinically, in the year elapsing between the first and second admissions, the patient's red cell count had dropped from 4,700,000 to about 3,000,00/cu. mm. The hemoglobin had dropped correspondingly. Associated with that drop we found a few nucleated cells in the peripheral blood. Whenever we see a moderately severe anemia accompanied by nucleated red cells in the peripheral blood we should suspect some myelophthisic process. That is the mechanism which I feel existed in this case. Just as an incidental curiosity, this patient had calcification and ossification of the mitral valve annulus, something we see quite frequently. But in the ossified annulus, there was some marrow tissue which also showed the presence of myelomatous tissue. We thereby have that evidence that the myleomatous process was quite diffuse.

The patient did die of renal failure, as Dr. Atlas pointed out, but the cause of it was the myelomatous process. The section of the kidney (Figure 4) strikingly revealed the presence of large, dense pink-staining casts filling many of the tubules. They are not recently formed casts, because around them we see a distinct foreign body reaction. The glomeruli are quite normal and relatively little inflammatory reaction can be seen in the stroma. This is no more than we would expect to find with this degree of tubular damage. It is a common concept that the presence of these obstructing casts causes renal failure on the basis of simple obstruction, but functional studies have shown that

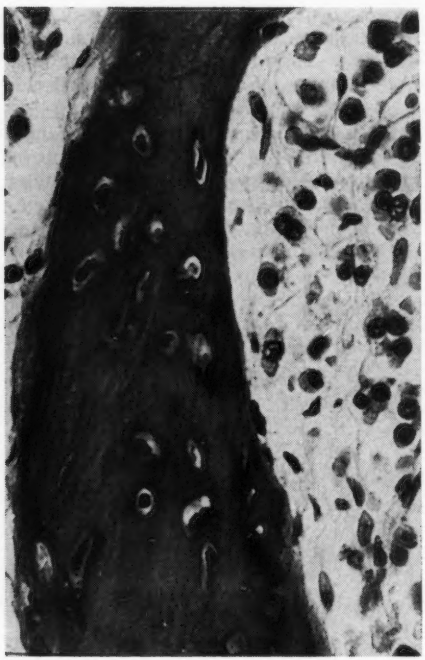

Figure 3: Vertebral marrow. Virtually all the cells are of the plasma cell lineage.

Figure 4: Myeloma casts in the kidney (pyramid). Observe the giant cell reaction about one of them.

there is also a disturbance in glomerular filtration, the nature of which is uncertain. According to Snapper, multiple myeloma affects the kidneys in approximately twenty *per cent* of the cases. It is almost invariably associated with excretion of Bence-Jones protein in the urine. A peculiar thing is that most cases of myeloma kidney are associated with normal blood protein. We seldom have hyperglobulinemia in those cases which develop the kidney complication.

Another complication of multiple myeloma that we observe in about twenty *per cent* of cases is the deposition of homogeneous, pink-staining material —amyloid—in atypical locations. The distribution is that of primary systemic amyloidosis rather than that of the more common type of secondary amyloidosis seen in chronic suppurative processes. A section of the myocardium revealed many enlarged muscle fibers. One section revealed primarily fibrous tissue, but within the fibrous tissue a homogeneous material was seen. The deposits in this instance were present in minute foci only and had no clinical significance. The deposition of amyloid is also frequently associated with the kidney complication of myeloma. The amyloid does not have the typical staining reaction of secondary amyloid and consequently some refer to it as para-amyloid. Presumably there is a chemical difference. Incidentally, the casts which were found in the kidney are not amyloid in nature.

The liver showed some mild fatty degeneration about the central lobular zone, a change which we regarded as toxic. There was a terminal bronchopneumonia. That is another frequent complication of multiple myeloma. In the process of developing and replacing the normal reticulo-endothelial elements, the tumor eliminates or reduces the body's capacity to form antibodies, and there is a reduced resistance to infection. This is a possible explanation for the frequency of these pulmonary complications. Another factor that has been mentioned is the increased viscosity of the blood due to the elevated globulin. This results in a reduced efficiency of the blood circulation.

Question: What were the findings in the pancreas?

Dr. I. Gore: There was a moderate, but insignificant degree of fatty infiltration. We find that quite the rule in the elderly age group.

Dr. I. Davidsohn:* It is now my duty to do a postmortem upon a postmortem, and I think that the postmortem itself was very well presented. The case is fairly clear now, but one question which members of this audience must always ask themselves is, "How could the diagnosis have been made?"

The most significant finding in this case was an anemia of about 3,000,000 red cells/cu. mm. with no leukocytosis and with two nucleated red cells. I have repeatedly stated here that whenever there are nucleated red cells in the presence of a moderate anemia this fact should be regarded seriously. It usually indicates neoplasm rather than fibrous myelosclerosis and means that something is developing rather rapidly. Almost invariably it is a neoplasm in the bone marrow. In this case it was a myeloma. This finding, however, was apparently not considered seriously enough.

It also appears that we have urinalyses done and pay little attention to them. We seldom pay much attention to what we obtain routinely, but when an operation is performed which usually causes urinary disturbances and the urinary findings are negative, we should take special note when a later admission reveals albuminuria. Unfortunately, we did not do a quantitative protein determination, but this change in the urinary findings may indicate that the protein which gave a two plus reaction may have been eliminated protein, and we saw some in the slides. There are some questions, however, which remain unanswered. We do not know why this patient suddenly had a normal, or rather low blood sugar.

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*Attending Pathologist and Director of Laboratories, Mount Sinai Hospital; Professor and Chairman, Department of Pathology, The Chicago Medical School.

Dr. Atlas tried to explain it, but perhaps if he sees more cases of multiple myeloma developing in patients with moderate diabetes he may see that again. It may be that those changes in the blood proteins have something to do with it, but that, of course, is pure speculation.

Multiple myeloma is now recognized as a neoplastic disease associated with disturbances in blood protein metabolism. It is probable that these protein substances are produced by the myeloma cells. The term "plasma cell myeloma" probably should be discarded, since the cells are probably not true plasma cells but myeloma cells, and according to those who have studied them they are transformed reticulum cells. There is in such cases a characteristic electrophoretic pattern of the blood proteins. There are rather steep curves in the region of the beta and gamma globulins, so characteristic that some people say it is probably diagnostic. It has been shown that there are actually two types of multiple myeloma. In one type, the cells resemble plasma cells and there is usually hyperglobulinemia but no Bence-Jones protein in the urine. In the other type, there is usually a very large amount of excreted Bence-Jones protein and relatively normal or slightly elevated total proteins, the elevated proteins being globulins.

Question: Was a microscopic study done on the pituitary gland?

Dr. I. Davidsohn: The pituitary gland was closely examined for evidence of metastatic lesions. I can assure you that there were no metastases in the pituitary. The hypothesis was very ingenious, but I do not think it applies here.

SCHOOL NOTES AND NEWS

The QUARTERLY would like to take this opportunity to welcome Dr. Richard H. Kosterlitz to the staff of The Chicago Medical School. Dr. John J. Sheinin has recently announced the appointment of Dr. Kosterlitz as Full-Time Instructor in Medicine.

Dr. Richard H. Kosterlitz

Dr. Kosterlitz comes to our school with an excellent background and a great deal of interest in teaching. He received his under-graduate training at the University of Illinois, and continued his medical education there, where he was awarded the degree of Doctor of Medicine in July, 1949.

Following this he served a two year Interneship at Cook County Hospital. Dr. Kosterlitz then received an appointment as Resident in Internal Medicine at the Veterans' Administration Hospital at Hines, Illinois, where he remained until July, 1953.

Other post-graduate work has included research in Physiology in the department of Clinical Science of the Graduate School of the University of Illinois College of Medicine under the direction of Drs. Andrew C. Ivy, and M. I. Grossman.

His most recent publication, "Fatty Inguinal Hernia," was published in the Illinois State Medical Journal in January, 1953. He has also published an article entitled "The Scalenus Anticus Syndrome" in the MD magazine in May, 1949.

Dr. Kosterlitz is a member of the Chicago Medical Society, Illinois Medical Society, American Medical Association, Scientific section of the Chicago Heart Association, and the Fellowship Committee of the Israeli Medical Society.

Prior to his entrance into Medical School, Dr. Kosterlitz served one year in the United States Navy Hospital Corps.

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It is with great pleasure that the QUARTERLY joins the administration, faculty, and student body of The Chicago Medical School in welcoming Dr. David T. Petty to our faculty as Full-time Associate in Surgery.

Dr. Petty was born in Istanbul, Turkey. His undergraduate education was received at the University of Chicago, where he was awarded the Bachelor of Science degree with a major in Physiology in March, 1943. He then attended Northwestern University Medical School, obtaining the degree of Doctor of Medicine in March of 1947.

He served his interneship at the United States Naval Hospital in Brementon, Washington, and following this remained on active duty in the Navy for two years as a Lieutenant in the Medical Corps of United States Naval Reserve. At one time he was medical officer in charge of the dispensary at Dutch Harbor, Alaska, and when this was inactivated, he served with the Alaskan Native Service at Unalaska.

Dr. David T. Petty

General Surgery is Dr. Petty's special field of interest. He had his residency training at the Veterans' Administration Hospital at Hines, Illinois, between 1950-1953. During this period he completed requirements for the degree of Master of Science in Pathology at Northwestern University, having started this work during a fellowship in Pathology at Cook County Hospital in 1949. The residency was briefly interrupted in 1950-1951 when he was recalled to active naval service at the outbreak of the Korean affair.

Dr. Petty has collaborated with Drs. Hans Popper and Hans Elias on several publications dealing with the anatomy and vascular supply of the liver. He is a member of the American Medical Association, the Chicago Medical Society, and the American Federation for Clinical Research.

FACULTY NEWS

Department of Anatomy

Dr. Leon H. Strong has recently been promoted to Professor of Gross Anatomy.

Dr. Hans Elias has been promoted to Associate Professor of Microscopic Anatomy.

Dr. Harold Koenig has been promoted to Associate Professor of Neuro-Anatomy.

Department of Biochemistry

Drs. A. R. Goldfarb and Leo Saidel have been promoted to Assistant Professor of Biochemistry.

Department of Dermatology and Syphilology

Dr. Silas Wallk has been named to the faculty as Instructor in Dermatology and Syphilology.

Department of Medicine

Dr. Samuel J. Taub, Professor of Medicine and Chairman of the Department of Allergic Diseases has started an allergy laboratory at the school which will function in cooperation with Dr. Richard Roberts, Professor of Biochemistry, Dr. James G. Shaffer, Chairman of the Department of Microbiology and Public Health, and Dr. William H. Shlaes, Instructor in Medicine and Research Physician at the Hektoen Institute. Research grants have been received and a long term research program has been initiated.

Drs. Jacob M. Epstein, Adauto Barbosa Lima, Chi Kong Liu, and Arthur J. Koven have recently been appointed to the staff as Clinical Instructors in Medicine.

Dr. Samuel A. Libert has been appointed to the faculty as Clinical Assistant in Medicine.

Dr. Clifford G. Pilz has recently joined the faculty as Clinical Associate in Medicine.

Department of Microbiology

Dr. Harold E. Elishewitz, Assistant Professor of Parasitology, has recently been elected President of the State Microscopical Society of Illinois, and has been appointed Fellow of the Societe Pathologic Exotique de Paris.

Department of Pathology

Dr. Kurt Stern, recently promoted to Associate Professor of Pathology, has

been appointed to the Advisory Editorial Board of the American Journal of Clinical Pathology.

Department of Physiology and Pharmacology

Dr. Piero P. Foa, Professor of Physiology, has been elected vice-President of the Chicago section of the Society of Experimental Biology and Medicine.

Dr. Ben B. Blivaiss has recently been promoted to Assistant Professor of Physiology.

Dr. Russell Hanson has been promoted to Associate in Physiology and Pharmacology.

Department of Psychiatry and Neurology

Dr. Harry H. Garner, Professor and Chairman of the Department, has recently been elected President of the Illinois Psychiatric Society.

Drs. Meyer Kruglik, LeRoy P. Levitt, and Klara G. Ranky have been promoted to Clinical Associates in Psychiatry.

Drs. Sherman E. Kaplitz and Louis Schlan have been promoted to Clinical Associates in Neurology.

Dr. Charles H. Shaiova has been promoted to Associate in Psychiatry.

Dr. Alfred Fein has been promoted to Clinical Instructor in Neurology.

Dr. Jacob H. Maltz has been promoted to Clinical Instructor in Psychiatry.

Recent appointments to the department include Dr. Eugene I. Falstein as Clinical Professor of Psychiatry and Dr. Adolf Haas as Clinical Assistant in Psychiatry.

Department of Surgery

Drs. David Fisher and Joseph N. Levenson have recently been appointed Clinical Instructors in Surgery.

Department of Urology

Dr. Morris Arnkoff has been appointed Clinical Associate in Urology.

ALUMNI NEWS

Class of 1933

Dr. Benjamin Sonenschein has been appointed to the full time staff of the Veterans' Administration Hospital in Phoenix, Arizona.

Class of 1935

Dr. Abe I. Podolsky has recently been appointed President of the State Board of Medical Examiners of the State of Arizona.

Dr. Isadore A. Sklar is now a member of the full time staff of the Veterans' Administration Hospital in Phoenix, Arizona.

Class of 1938

Dr. Alvin A. Hoffman has recently announced the opening of his office in York, Maine.

Class of 1942

Congratulations to Dr. and Mrs. Samuel Cohen on the birth of a daughter, Arlene Cyd, on September 2, 1953.

Dr. Frank C. Starpoli has recently been initiated a Fellow in the American College of Surgeons.

Dr. Seymour D. Wishnick has recently passed the examinations for licensure in the State of California.

Class of 1944

Dr. Milton Wohl is presently serving as a Resident in Orthopedic Surgery at the Strong Memorial Hospital, University of Rochester, New York. Dr. and Mrs. Wohl are to be congratulated on the birth of a daughter, Lisa, on November 22, 1953.

Class of 1946

Dr. Sidney Malitz, a former Editor-in-Chief of the QUARTERLY, has recently informed us of his certification in Psychiatry by the American Board of Psychiatry and Neurology. Dr. Malitz was discharged from the Army this past January, having served at the Neuropsychiatric Division of the Medical Service Graduate School at the Walter Reed

Army Medical Center, Washington, D. C. He has now returned to his post as Senior Research Psychiatrist at the Psychiatric Institute of the Columbia - Presbyterian Medical Center, New York City. Dr. Malitz is co-author of an article on "The Serial Use of the Amytal Test in the Diagnosis of Organic Brain Disease" in the February, 1954 issue of the Archives of Neurology and Psychiatry.

Class of 1947

Dr. Melvin L. Goldy is presently on active duty in Korea with the United States Army Medical Corps.

Dr. Edward P. Svetkey is now practicing in Scarsdale, New York, after having recently been discharged from military service, during which time he received the Bronze Star medal.

Dr. Seymour Warman has recently returned from service and has now opened offices at 1272 Grand Concourse and 1391 Pelham Parkway North, Bronx New York.

Class of 1949

Congratulations to Dr. and Mrs. Marshall Persky on the birth of their daughter, Gail Jo, on February 14, 1954.

Dr. Nerissa P. Singh has been appointed Instructor in Pediatrics at the University of Illinois College of Medicine and has opened an office at 5616 South Drexel Avenue, Chicago, Illinois.

Class of 1950

Congratulations to Alfred R. Moldovan on the occasion of his marriage to the former Miss Jean Sorkin on December 27, 1953.

Dr. Joseph B. Vesce has recently been appointed to the Medical Service of Saint Peters Hospital, Brooklyn, New York.

Dr. J. Marvin Wertheim has recently been appointed Chief of the Medical Service at the United States Army Hospital at Fort Hamilton, New York.

Class of 1951

The QUARTERLY recently received a highly gratifying letter from Dr. Joseph T. Findaro. We were impressed by this letter not only because of the nice things that he had to say, but because he took the trouble to write to us to keep us informed of his activities. Dr. Findaro writes, "It was quite interesting reading about my former classmates in your last publication. I have been in the Navy since August, 1952 and had been assigned to the Bethesda Naval Hospital in Maryland, until June, 1953. At the present time I am the Medical Officer (Lt.j.g.) aboard the USS Vulcan." Congratulations to Dr. Findaro on the occasion of his recent marriage to the former Miss Patricia Ann Paduano, of Woodside, Long Island, New York.

We were also very happy to hear from Dr. Sanford I. Gaylord, who is now a Resident in Medicine at the Mount Sinai Hospital of Cleveland, Ohio. We wish to congratulate Dr. and Mrs. Gaylord on the birth of their third child, Gregg Michael, on January 13, 1954.

Class of 1952

Lieutenant j.g. George Ehrlich of the staff of Commander Destroyer Squadron Thirty-two has recently been appointed Squadron Medical Officer aboard the USS Rowe.

Dr. Harold B. Fein is now associated in practice with Dr. A. Shayevitz at 102 Main St., South River, New Jersey.

Dr. Marion J. Finkel is now serving as Assistant Resident in Medicine at New York University post - Graduate Fourth Medical Division at Bellevue Hospital, New York City.

Congratulations to Dr. and Mrs. Arnold Grier on the birth of their son, Kenneth Scott, on December 26, 1953.

Congratulations to Dr. Sidney Schuchter on the announcement of his recent marriage to the former Miss Doris Brown of Chicago, Illinois. Dr. Schuchter is presently a Resident in Medicine at the Cleveland Clinic, Cleveland Ohio.

STUDENT NEWS

Class of 1954

Best wishes to Arnold Adicoff of the Bronx, New York, and the former Miss Ruth Kahn of Milwaukee, Wisconsin, on the occasion of their marriage, March 27, 1954.

Congratulations to Marvin Keller of the Bronx, New York, and the former Miss Shirley Eichel of Chicago, Illinois, on the occasion of their marriage on March 28, 1954.

Class of 1955

Congratulations to Seymour and Shirley Bradus on the birth of their daughter, Joan Lori, on March 5, 1954.

Best wishes to Elliott Breslar of Belle Glade, Florida, and the former Miss Roberta Fine of Chicago on the occasion of their marriage on March 20, 1954.

Congratulations to Milton and Janice Greenberg on the birth of their first son, Stewart York, on January 23, 1954.

Class of 1956

Congratulations to Jesse S. Gochman of Paterson, New Jersey, on the announcement of his engagement to Miss Frances Flower of Peekskill, New York. The wedding will take place in June

Best wishes also to Evan Katz of New York City and Miss Janet Wacht of New York City on the announcement of their engagement. The wedding is planned for June.

Best wishes to George B. Perlstein, Jr. of Chicago, Illinois, and the former Miss Mary Adler of Shaker Heights, Ohio, on the occasion of their marriage on December 20, 1953.

Congratulations to Daniel Schildkraut of New York City and the former Miss Ardis Evelyn Craine on the occasion of their marriage on January 1, 1954.

Congratulations to Jack Schnee of New York City on the announcement of his engagement to Miss Sandra Salmanowitz of New York City. The wedding will take place in June.

Class of 1957

Congratulations to Norman H. Cohen and Miss Evelyn L. Starker of Brooklyn, New York, on the announcement of their recent engagement.

Best wishes to Ben Nitzberg of the Bronx, New York, and to the former Miss Zed Becker of the same city on the occasion of their marriage on March 23, 1954.

Best wishes to Ray Reich of New York City, and the former Miss Audrey Lorek of Chicago, Illinois, on the occasion of their marriage on December 31, 1953.

Congratulations to Arthur L. Teplitzky of Brooklyn, New York, and the former Miss Estelle R. Levin of Philadelphia, Pennsylvania, on the occasion of their marriage on March 28, 1954.

ORGANIZATION NEWS

Student Council

Another quarter has passed and the Student Council can again look back on several accomplishments and ahead to several promising ideas.

During the winter quarter, copies of the Student Directory were again distributed to the members of the student body who are in good standing. The Directory was produced at great effort and was made as accurate as circumstances permitted.

At present, discussions are being conducted and a study is being made by Student Council, as to the best way of acquiring a modern mimeograph machine for the use of the student body. It is hoped that such a machine can be acquired in the near future.

Again we repeat that any member of the student body may attend, and is cordially invited and urged to attend, any or all Student Council Meetings, and to participate in all discussions.

Phi Lambda Kappa

During the past months Phi Lambda Kappa Fraternity has continued the social and educational programs which have always marked our organization.

At the first meeting of the quarter, our delegates to the Annual National Convention gave a report on what had taken place at the convention, which last year was held at the Southern Hotel in Baltimore on December 29, 30, and 31, 1953. They reported on the many worthwhile programs which the national organization is engaged in, and upon the success which we achieved in equipping the new Phi Lambda Kappa Medical Library at the Hebrew University Medical School in Israel. At this convention, we of Alpha Rho Chapter were awarded a cup as the outstanding under-graduate Chapter during 1953. We hope to continue this record in 1954.

On January 22, we held an informal gathering at the Illini Union. This affair was run in conjunction with the Alpha Alpha Chapter at the University of Illinois.

The Annual Induction Dinner was held on Sunday January 31, at the Sheridan-Plaza Hotel. A large number of members and alumni were present to initiate and welcome our new members into Phi Lambda Kappa.

The grand ballroom of the Graemere Hotel was the scene of a dance and show sponsored by Phi Lambda Kappa on February 21, 1954. There was dancing, refreshments, and an entertainment program sponsored by the Ladies' Auxiliary.

This year we hope to have the most successful Senior Dinner-Dance in our history. This affair will be held on May 29, 1954, at the Tam O'Shanter Country Club.

Phi Delta Epsilon

The Beta Tau Chapter of Phi Delta Epsilon has had a very active program this year. The Annual Convention held in Baltimore, Maryland, last December, was attended by over one thousand delegates and friends. On January 8, 1954, a Pledge Luncheon was held at the Illini Union in honor of the pledges of the Beta Tau Chapter. A very good attendance helped make this an enjoyable affair. Future luncheon meetings are being planned.

The Annual Tri-Chapter Dinner Dance was held at the Furniture Club on February 20, 1954. Among the initiates was Dr. Harry H. Garner, Professor of Psychiatry. Recently the graduating members of the fraternity were honored at a dinner given by the Alumni at the Furniture Club.

Plans for the future include a Senior Dinner-Dance to be held in May.

Association of Internes and Medical Students

The Association of Internes and Medical Students, for the remainder of the Winter and Spring Quarters, has planned a full program of interesting speakers and activities. The speaking schedule will cover a wide variety of topics dealing with medical practice in this country, foreign medicine, health in Chicago, academic medicine, and other topics of current interest. In addition, social evenings open to all students are being planned for the very near future. The noon hour musicales will continue, with greater frequency if possible. There are also several activities planned which are designed to be of service to the student body.

All in all we hope to bring to the student body and members a well rounded program which we feel can be embraced by all medical students.

Student American Medical Association

Next fall SAMA's new life insurance plan will become available. The proposed program will provide $5,000 annually renewable term life insurance for all student AMA members desiring it at a cost of $25.00 per annum. The premiums would be waived in case of total disability. After completion of internship or at an age to be determined, a $5,000 straight life policy would be made available at regular prevailing rates for this type of coverage.

Further details can be found in recent and forthcoming issues of the Student A.M.A. Journal.

BOOK REVIEWS

MECHANISMS OF UROLOGIC DISEASE by David M. Davis, M.D. Cloth. First edition. 156 pages with 6 figures. Philadelphia and London: W. B. Saunders Company, 1953. $4.50.

Dr. Davis, collaborating author with Dr. Hugh H. Young of the original "Practice of Urology," has written this brief volume utilizing his introductory Urology lecture notes at the Jefferson Medical College and has intended it for the beginner and for those physicians who are not urologic specialists. It is the author's opinion that an intimate knowledge of the natural history, clinical course, and proper treatment depends on the knowledge of the physiologic processes and pathologic changes involved, much more than on a knowledge of anatomic arrangements. In emphasizing these features he presents a bird's-eye view of the entire field and stresses the results of urinary tract obstructions. The chapter on obstructions is by far the best one in this concise volume and it alone makes the book a valuable addition to any physician's library.

The other chapters, while being somewhat brief, are of enough scope to offer a rapid review of the subjects covered. An effort has also been made to supply adequate and up-to-date references to the literature, as well as a list of standard works of reference, for, as the author states, "Urology is a subject in which there is enough variety of opinion so that no one textbook should be used exclusively."

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PERIPHERAL NERVE INJURIES by Webb Haymaker, M.D., and Barnes Woodhall, M.D. Cloth. Second Edition. 333 pages with 272 illustrations. Philadelphia: W. B. Saunders Company, 1953. $7.00.

One cannot help but be impressed by the numerous illustrations and diagrams in this book. These diagrams are simple, readily interpreted and, happily, placed near the corresponding text material. The book concerns itself primarily with the examination, classification, causes, and symptoms of peripheral nerve injuries. The treatment of these injuries is not discussed. Although the authors' intention to stress early recognition of peripheral nerve injuries is admirably accomplished, a short chapter on the general principles of immediate management would be welcome. The organization of the subject matter and the very adequate index make this an ideal quick reference book for the orthopedist, neurosurgeon, and general surgeon.

* * * *

ESSENTIALS OF MEDICAL DIAGNOSIS by Rt. Hon. Lord Horder, M.D., and A. E. Gow, M.D. Cloth. Second Edition. 462 pages with 23 plates, 6 in color, 22 figures in the text and 5 charts. Baltimore: The Williams and Wilkins Company, 1953. $6.00.

This wonderful book should be read by all second and third year medical students. The sections on physical diagnosis are particularly well-done. The text is divided into several major sections including general principles, the nervous, cardiovascular, respiratory, digestive, and urinary systems, blood and blood-forming organs, the joints, ductless glands, skin, and pyrexia. In each section, the anatomy and physiology is briefly reviewed, often with illustrations. Then, physical examination of that system is described. The differential diagnosis of common symptoms referable to that system is adequately discussed. Instrument examination of the system is described and laboratory and X-ray findings are presented. This is the second edition and many revisions have been made. The sections on blood, jaundice, the liver, and the urinary system have been rewritten to include the vast advances that have been made since 1928, when the first edition appeared. This book is highly recommended to the medical student.

* * * *

ESSENTIALS OF INFANT FEEDING FOR PHYSICIANS by Herman Frederic Meyer, M.D. Cloth. 249 pages with 13 illustrations. Springfield: Charles C. Thomas, 1952. $7.75.

This concise and practical book presents the principles of infant feeding in a manner such that they may be readily applied. The vast number of products available for infant feeding have been classified and listed according to their composition and clinical uses. Adequate discussions of the problems of the mechanics of infant feeding, breast feeding, "demand feeding," and feeding problems are included. There is a complete newborn hospital nursery routine given in detail. A very valuable appendix includes tables of measurement; tables of vitamin and calorie and chemical content of milks; relative costs of various milk formulas and vitamin preparations; methods of parenteral fliud administration; and a suggested sequence of solid food additions to the infant diet. The book is highly recommended to the pediatrician, general practitioner, and medical student.

* * * *

CONDUCTION ANESTHESIA by George P. Pitkin, M.D. Edited by James L. Southworth, M.D., Robert A. Hingson, M.D., and Winifred M. Pitkin, M.D. Second Edition. Cloth. 1005 pages with 585 illustrations. Philadelphia: J. B. Lippincott Company. 1953. $22.50.

Since the appearance of the first edition of this book in 1946, it has become a standard text in its field. It is edited by a surgeon, anesthesiologist, and clinician-anatomist team in a way such that physicians in either specialty may better understand the problems of the other. Chapters and material have been added on the vertebral canal and its contents, topical anesthesia for the

ophthalmologist, the oral and general surgeon, and the complications of conduction anesthesia and their prevention. The sections on pharmacology have been revised. There is an extensive bibliography of fourteen pages and indices of authors and subjects. This book deserves a place in all medical libraries and in the collections of anesthesiologists.

* * * *

HORMONAL AND NEUROGENIC CARDIOVASCULAR DISORDERS by Wilhelm Raab, M.D. Cloth. 722 pages with 87 figures and 21 tables. Baltimore: The Williams and Wilkins Company, 1953. $15.00.

Despite the advances made in clinical and experimental endocrinology in the last few decades, the correlation of neuroendocrine knowledge with clinical cardiology has not been sufficiently appreciated. Dr. Raab has accumulated and integrated a prodigious quantity of information from the literature and presents the material in an easy-to-read, logical and thought-provoking manner. This is the first attempt to relate the complex of endocrine and neurohormonal physiopathology with functional and structerial in an easy-to-read, logical, and thought-that has appeared in the literature. It is a monumental work and the bibliography of over 3000 references is only partial testimony of this fact. "The future of cardioangiology in theory and practice," says Dr. Raab, "will largely depend on a growing insight into its intimate relationships with neurohormonal and hormonal biochemical functions." This book should do much to stimulate the "growing insight" to which Dr. Raab refers. It deserves a place in the library of the physiologist, the internist, and the cardiologist.

ANATOMY AND SURGERY OF HERNIA by Leo M. Zimmerman, M.D. and Barry Anson, Ph.D. (Med. Sc). Cloth. 374 pages. Baltimore: The Williams and Wilkins Co. 1953. 10.00.

Several outstanding features mark this work as a classic in the field of herniology. Both authors are thoroughly and well-versed in the subject matter, rendering an historical, academic, and functional approach to the problems of hernia. The historical approach is not only of hernia *per se* but of medicine in general and serves as a background to the surroundings and circumstances which either helped or impeded the progress toward the modern concepts and treatment of hernia. The exposition of the anatomy is first of the general regions of the various herniae. This anatomy is thorough and clear. The pathologic anatomy of the hernia becomes quite understandable and actually could only have evolved upon the basis of the thorough anatomical and historical background presented. The absolutely different pathologic anatomy of the direct and indirect inguinal herniae is made clear and the evolution of the treatment of each by the authors' logical technique is well-presented. The exposition of the internal herniae based upon their embryologic background is historically traced and well-illustrated with drawings. Other herniae are presented in complete detail, such as the femoral, obturator, umbilical, diaphragmatic, pelvic, and ventral. "The central theme. . . has been the effort to re-direct the thinking of surgeons to the actual lesion present in the various types of hernia and to develop logical measures for correcting these defects without sacrifice of important physiological structures." This is well-done, clearly presented, easily read, and because of the common frequency of hernia is an important contribution.

David M. Movitz, M.D.

ABSTRACTS SECTION

FOA, PIERO P., MAGID, EDWARD B., GLASSMAN, MORTON D., and WEINSTEIN, HARRIET R. *(Department of Physiology and Pharmacology).* Anterior Pituitary Growth Hormone (STH) and Pancreatic Secretion of Glucagon (HGF). Proc. Soc. Exp. Biol. and Med., *83*:758, 1953.

Fourteen cross-circulation experiments were performed by anastomosing the pancreatico-duodenal or a mesenteric vein of a donor *dog D* with a femoral vein of a recipient *dog R*. The intravenous injection of purified anterior pituitary STH into a normal donor or into a donor previously treated with the same STH causes the appearance of a hyperglycemic material (glucagon) in the blood of the pancreatic but not of the mesenteric vein. This glucagon causes hyperglycemia in a normal recipient dog. In addition to decreasing insulin secretion, and inhibiting peripheral utilization of glucose, STH appears to cause hyperglycemia by stimulating the secretion of glucagon by the pancreas. It is believed that these results further support the hypothesis that glucagon is a pancreatic anti-insulin hormone contributing to the maintenance of a normal sugar concentration.

* * * *

HARING, OLGA M. *(Asst. in Med.)*, LUISADA, A. A. *(Assoc. Prof. of Medicine and Director, Division of Cardiology).* Studies with Intravenous Gitalin I-Clinical and Electrocardiographic Observations, Amer. Heart Journal, *45*:(1), 108-121, January, 1953.

Intravenous administration of gitalin, a glycoside of *Digitalis purpurea*, was studied in sixteen ambulatory patients with various degrees of congestive failure, and in four control subjects. Clinical and electrocardiographic observations are reported. Comparison with strophanthin, lanatoside C, and digitoxin was made.

Initial intravenous dose was found to be between 2.5 and 3.0 mg.; total digitalizing dose, from 5.0 to 6.0 mg. Two injections at twenty-four hour intervals were sufficient to digitalize the average ambulatory patient. Maintenance was obtained with two weekly injections of 2.5 mg. Administration of the drug caused no appreciable side effects. Two difficult clinical cases who tolerated poorly other glycosides showed great tolerance toward gitalin and obtained beneficial results from its use.

The wide margin of safety, the relative lack of side-effects, and the rapid elimination indicates gitalin as the drug of choice in cardiac failure caused by rheumatic carditis or coronary heart disease, and in cases with ectopic ventricular rhythms. Ambulatory patients need frequent checking on account of the rapid elimination of the drug.

* * * *

LUISADA, ALDO A. *(Assoc. Prof. of Med.)*, and CONTRO, S. Modifications of the Heart Sounds in Bundle Branch Block. J. of Mt. Sinai Hosp., Vol. 19, 1952.

A phonocardiographic study was made of twenty-four cases of complete heart block, and:

(1) The second heart sound was split in twenty-two cases and prolonged in the other two, as a result of ventricular asynchronism.
(2) The first heart sound was prolonged in all cases; it was of poor amplitude in seventy-three *per cent* of cases of left bundle branch block and in fifty-five *per cent* of cases of right bundle branch block.
(3) In none of the observed cases was there a splitting of the first sound. On the other hand, a division of this sound into three groups of vibrations was observed in two cases with left bundle branch block and intraventricular block.
(4) The mechanism of production of the first sound is discussed and the theoretical impossibility of its splitting by bundle branch block is stressed.
(5) The possible influence of additional ventricular lesions (*i.e.*, blocks, hypertrophy) or hypertension in one of the great vascular systems on the changes of the heart sounds, is further discussed.

* * * *

MILLER, DONALD S. *(Prof. and Chmn. Div. of Ortho. and Traumatic Surg.)*. Brachial plexus injuries associated with the traumatic shoulder joint. Ill. Med. Jour., *103*:299-304, May, 1953.

Fractures, dislocations, and injuries of the shoulder joint region are occasionally associated with tears, avulsions, or local traumatic hemorrhages in and about the nerve roots or cords of the brachial plexus. These complications should be treated after a careful and early examination of the peripheral nerves of the upper extremity, with an evaluation of the nerve roots involved. Careful progress notes should be recorded. Early treatment by immobilization in slight abduction, faradic and galvanic stimulation of muscle, as well as proper physical therapy, are necessary.

Complete brachial plexus injuries, with neurovascular phenomena and total paralysis of the extremity may require reconstructive operation of the joints (fusion of the shoulder and elbow), or amputation at the shoulder joint.

Although the incidence of brachial plexus injuries in children is rare, several cases are noted in this series with severe, residual paralysis resulting.

* * * *

REICH, WALTER J., RUBENSTEIN, M. W., NECHTOW, M. J., and REICH, J. B. *(Dept. of Ob. and Gyne.)*. Diagnosis and Management of Abnormal Uterine Bleeding, J.A.M.A. *152*:1679-1682, Aug. 29, 1953.

Abnormal uterine bleeding must be regarded seriously no matter in what age group this symptom is found. It may be easier to arrive at the cause of bleeding when the anatomicopathological pattern is kept in mind. Above all, carcinomas must be foremost in the differential diagnosis of any abnormal bleeding.

Blood studies should be done in all cases of abnormal uterine bleeding, irrespective of the obvious gynecological disease, to rule out dycrasia. Erosions of the cervix should not be treated

until the diagnosis of carcinoma has been disproved by smear and biopsy. All patients with cervical polyps who have abnormal bleeding should have a curettage in addition to a polypectomy so as not to overlook a concomitant carcinoma higher up in the uterus. Patients with asymptomatic fibroids who start abnormal bleeding should be thought to have a possible commitant carcinoma. One must be cognizant of the possibility of the existence of fibroids with concomitant carcinoma of the ovary.

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REICH, W. J., NECHTOW, M. J., SILVERMAN, H. E., KURZON, A., REICH, J. B., and RUBENSTEIN, W. M. *(Dept. of Ob. and Gyne.)*. Artificial Vagina, AMA Archives of Surgery. *66*:129-136, February, 1953.

The management of congenital absence of the vagina is discussed. A method embracing the use of (a) a simple plastic vaginal form with a built-in irrigating system, (b) complimentary use of oral and local estrogenic substances to expedite healing and vaginal epithelization, (c) prolonged post-operative self-dilation with graduated plastic dilators, is outlined.

The surgical technic is described in detail. The important step in this procedure is the vertical incision through the perineal body. This provides a larger orifice through the vaginal space and appears to be a significant factor in diminishing contraction.

* * * *

SHAFFER, J. G. *(Professor of Microbiology)*, et al. Factors Affecting the Propagation of *Endamoeba histolytica in vitro* in the S-F Medium and in Tissue-Bearing Substrate. Annals of the N. Y. Academy of Sciences, *56*:1033-1047, October, 1953.

Certain physical and chemical factors in the Shaffer-Frye (S-F) medium and in the tissue-bearing substrate were investigated to see what effect each exerted on the propagation of *E. histolytica*. It was found that anaerobiosis, pH, horizontal surface area, and temperature were important to control. No investigations of oxidation-reduction potentials were made. Of the chemical factors, it was found that dextrose or maltose was essential, there being a direct correlation between propagation of the amoebae and the concentration of these carbohydrates, within the limits used. The peptone in the S-F medium was found to be critical since no substitute for trypticase was found. There was also a direct relation between the *per cent* of normal horse serum in the S-F medium and propagation of the amoebae up to a ten *per cent* concentration, above which the serum appeared to be toxic.

The bacterial cell was found to be of the most critical importance in the S-F medium, there being a direct relation between the number of bacterial cells in the medium and propagation of *E. histolytica*. Evidence was presented indicating that soluble metabolites of bacteria were not responsible for propagation of the amoebae.

Certain differences between conditions in the S-F medium and the tissue-bearing substrate were pointed out.

SHAFFER, J. G. *(Professor of Microbiology)*, SIENKIEWICZ, H. S., and WASHINGTON, J. E. The Propagation of *Endamoeba histolytica* in Tissue-bearing Culture without accompanying Bacteria or other Microorganisms, Am. J. of Hygiene, *57*:366-379, May, 1953.

Successful propagation of *Endamoeba histolytica* was obtained in a tissue-bearing culture containing minced chick embryo tissues suspended in ten *per cent* concentration in Hank's tissue culture fluid. Four different strains of the amoeba were maintained through forty serial forty-eight to seventy-two hour transplants. No bacteria or other microorganisms were found in any of the transplants by any technique used. Routinely, whole nine to eleven-day chick embryos were used in these transplants.

Further experiments revealed that when individiual tissues were utilized, liver proved to be most active in supporting propagation of the amoebae, with brain, gut, heart, and skeletal muscle following in that order. It was found that tissues of embryos of four to fourteen days incubation would support propagation, with the older embryos being most active.

No propagation of *E. histolytica* occurred when thoroughly ground tissues containing no intact cells were substituted for the minced tissues. Further evidence indicated that fresh, intact tissue cells were essential to the propagation of the amoebae.

It was found that the trophozoites of *E. histolytica* would enter blocks of four to five day chick embryo tissues, liver lobes, and hearts of nine to eleven day embryos, but not brain or skeletal muscle, if placed in the cultures. Stained sections of these tissues showed the amoebae present even among the tissue cells. No evidence was seen to indicate that the amoebae damaged the tissue cells.

* * * *

SHUBIK, PHILIPPE, and RITCHIE, A. C. *(Division of Oncology)*. Epidermal Carcinogenesis in the Mouse Induced by One, Two, or Three Applications of 9, 10-Dimethyl 1-1, 2-benzanthracene Followed by Repeated Applications of Croton Oil. A New Hypothesis of the Mechanism of Carcinogenesis. Cancer Research, *13*:343-346, 1953.

A single application of a carcinogenic hydrocarbon followed by repeated applications of croton oil can be used to induce tumors in the skin of the mouse; it has been noted previously that increasing the concentration of the carcinogen used in the single application increases the total yield of tumors produced. In the present experiments it has been noted that increasing numbers of applications of a carcinogen, either one, two, or three at a constant concentration, followed by croton oil treatment does not lead to a similar increase in the number of tumors induced, and may result in a decrease. Reasons for this are discussed, and the possible induction of a refractory state by the carcinogen considered.

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